EXTENT AND TIME OF BLOOD-LOSS AFTER CIVILIAN INJURY

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THE prevention and treatment of "wound shock" after injury requires an estimate of the bleeding so that whole blood may be safely and accurately given (Clarke 1959). Accurately timed replacement can make anæsthesia and surgery possible and less dangerous, reduce many of the dangers of oligæmia and anæmia, and shorten convalescence. Early assessment allows more time for accurate cross-matching, and makes emergency transfusion safer. It is also necessary to know the rate of bleeding into the dressing and the tissues after primary treatment. The timing of transfusion should be determined by the time of bleeding.

Plasma-volume studies on battle casualties of the First World War (Keith 1919) confirmed by similar studies in the Second (Chute et al. 1945, Grant and Reeve 1951) showed that most injured patients lost more blood than had previously been recognised. Further evidence was provided by the American research team in Korea (Prentice et al. 1954) when an attempt was made to replace blood-loss completely with transfusions of pooled group-O blood.

The increasing use of whole-blood transfusions and the obvious resulting clinical benefit has dissipated earlier suspicions that blood-volume evidence was unreliable or that blood was not really lost but sequestered in the capillary bed.

The data on the volume of blood lost in civilian injuries are more meagre. Noble and Gregersen (1946) measured blood-loss by plasma-volume studies in 19 patients two to nine hours after admission; in 4 of them observations were repeated a few hours later. Evans et al. (1944a) provided data on the first nine hours after injury. Clarke, Topley, and Flear (1955) measured blood-loss in 40 patients in the first to fourth day after civilian injuries and found a further fall in red-cell volume after the first day in most of them.

Noble and Gregersen (1946) attempted to correlate the amount of bleeding with the number of closed major fractures. Grant and Reeve (1951) measured the volume of damaged tissue in war wounds and attempted to correlate the amount of bleeding with the size of the wound. Clarke and his colleagues (1955) measured the volume of swollen limbs in order to introduce improved methods of assessing clinically the amount of bleeding from the nature of the wound.

In this paper we report on the time of bleeding after civilian injuries, based on repeated estimations of red-cell volume, and on total blood-loss associated with different types of civilian injury.

Material and Methods

We studied 107 patients (91 men and 16 women, aged 15–84 years) injured mostly on the roads or at work. On 50 of the patients red-cell and plasma-volume estimations were carried out together with detailed clinical observations (Fisher 1958); and on 57 patients one or more estimations were made at a time most likely to provide evidence of the extent of blood-loss. Information is also included on 33 patients previously reported (Clark, Topley, and Flear 1955). On 39 patients three to six estimations were performed, on 36 two, and on the remaining 65 one only. In only 6 of the 140 patients was there evidence of pre-existing disease; in them the apparent early blood-loss was probably exaggerated by an initial anæmia.

The patients were selected primarily because bleeding was likely to exceed one litre, and it was feasible to estimate the blood-volume at least once.

Measurement of Blood-loss

Blood-loss was estimated from direct and indirect measurements of the volume of circulating red-cells making allowance for blood transfused. The initial loss was derived from the difference between the estimated red-cell volume and the "expected normal" for the patient's height (Topley and Jackson 1957). In the 33 earlier cases the "normal" value was derived from weight and follow-up red-cell volume.

$$\text{Initial blood-loss} = (\text{Normal red blood-cell volume} + \text{red cells transfused} - \text{red blood-cell volume found}) \times \frac{100}{40}$$

Estimates of later loss were deduced from differences between red-cell volumes reported at intervals of hours or days—i.e.,

$$(\text{Previous red blood-cell volume} + \text{red cells transfused} - \text{red blood-cell volume found}) \times \frac{100}{40}$$

It was assumed that each bottle of blood transfused supplied 170 ml. of red cells, and, when converting red-cell loss to whole blood, that the lost blood had a hæmatocrit value of 40%.

Red-cell volumes were measured directly, with red cells labelled with radioactive phosphorus (^{32}P) or chromium (^{51}Cr).

In 48 of the 300 estimations, red-cell volumes were measured indirectly from the plasma volume and venous hæmatocrit, with T.1824 (Evans blue) as a plasma label. This method, though quicker, is less accurate than the direct method and was usually used only for the initial estimation. Details of the methods are described by Davies and Topley (1959).

Blood lost at operation was measured when possible by weighing swabs or by measuring the contents of the suction bottle. Other external blood-loss was assessed visually and changes in swelling and presence of bruising in closed injuries taken as a guide to internal bleeding.

Transfusion Management

The amount of blood to be transfused was decided by the surgeon according to the state of the patient. The results of red-cell volume studies were at times taken into consideration, particularly in deciding the total volume to be transfused in very severe injuries. In some patients red-cell volume estimations made possible a partially controlled trial of two levels of transfusion (Topley and Fisher 1956).

Results

The measurements in figs. 1 to 5 which contain details of representative patients give the total amount of blood lost by different injuries and when it was lost. Average figures are given in the table for groups of patients with similar types of injury.

In a few patients the measured loss was negligible. This often was compatible with the clinical findings. In the other patients the extent of blood-loss appeared consistent with the nature of the injury, the extent of visible bleeding, the evidence of deep-tissue damage, and the bleeding

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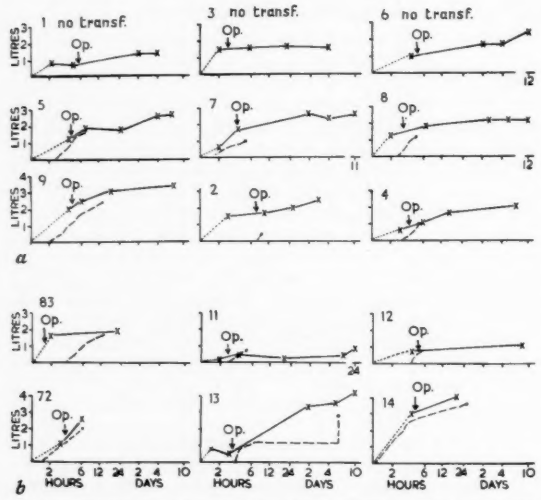

Fig. 1—Amount and time of blood-loss (continuous line) and blood transfused (broken line) in patients with *(a)* fractures of the tibia and fibula *(b)*, and severe open wounds of the leg.

revealed at operation. The exceptions to this were few and are discussed in the section on the accuracy of the red-cell-volume estimations.

BLOOD-LOSS FROM DIFFERENT SITES OF INJURY

Fractures of Tibia and Fibula (fig. 1a)

Limb measurements (Clarke, Topley, and Flear 1955) and hæmoglobin studies had suggested that most simple closed fractures of both bones of the leg, without gross swelling, do not lose more than $^1/_2$–1 litre (1–2 pints) of blood. Fractures with comminution of the bones and greater soft-tissue injury lose more and such patients were included in this study (fig. 1*a*). There were 4 closed fractures, and 9 open ones with mild to moderate skin damage. All were treated by primary internal fixation with metal plates. Skin grafting was necessary in 2 patients (e.g., patient 9, fig. 1). A tourniquet was usually used during operation and bleeding was then negligible. Without it, losses of 0·7 litre, 0·3 litre, and 0·8 litre were measured.

In the 12 patients in whom total blood-loss was measured later than twenty-four hours after injury, it averaged 2·1 litres; in only 1 was the measured loss less than 1 litre, in 3 between 1 and 2 litres, while in 2 others the total loss exceeded 3 litres (see table).

In 7 patients estimations were carried out before operation (two to four hours after injury), after operation (four to ten hours after injury), and four to eight days later. The average preoperative loss was 1·2 litres; the postoperative estimation 1·8 litres; and total loss 2·4 litres. Thus half the loss occurred within two to four hours, and a quarter after the postoperative estimation.

Severe Open Wounds of Leg (fig. 1b)

The nature of injury and the extent and time of bleeding varied much more in these patients. Injuries included severe open fractures requiring amputation (e.g., patients 11 and 12) and flaying injuries requiring skin grafting (e.g., patients 72 and 13). A tourniquet was used during operation in 2 patients only.

In the 4 amputees the total blood-loss ranged from 0·5 to 4·9 litres. In 3, further estimations were carried out; in all the postoperative blood-loss was small. For example, in one case blood-volume was first estimated 24 hours after injury, by which time 3 litres of blood had been lost. Operative blood-loss was considerable since the whole calf was explored before making the decision to amputate; but later blood-loss was negligible (0·2 litre).

3 flaying injuries all involved at least the total area from knee to ankle, with a blood-loss of 2·5 to 3·6 litres. In the 2 patients on whom repeated estimations were performed a different pattern of blood-loss was observed (patients 72 and 13). In both the initial loss in the first three hours was comparatively small (0·4 and 1·1 litres) compared with a total loss of 3·6 (five days) and 2·5 litres (six hours).

TOTAL BLOOD-LOSS 1–15 DAYS AFTER SELECTED INJURIES (NO. OF PATIENTS)

Nature of injury	0–0·9 l.	1–1·9 l.	2–2·9 l.	3–3·9 l.	4–4·9 l.	5–5·9 l.	⩾6 l.
Fractures:							
Tibia and fibula ..	1	3	6	2	..	..	..
Shaft of femur (closed)	3	5	3	..	1	..	..
Shaft of femur (open)	..	2	1	1	1	..	..
Pelvis (closed) ..	1	..	2	1	1	..	..
,, (open)	..	..	..	..	..	1	1
Crushed chest injuries ..	1	1	7	2	..	..	..
Severe hand injuries ..	..	2	2	..	1	..	..

Fractures of Femur (fig. 2)

18 patients had fractures of the femoral shaft; 12 had closed fractures treated by traction. 3 open fractures were treated by traction, and 3 by primary internal fixation. The total blood-loss in the closed fractures averaged 1·8 litres (range 0·4–4·7 litres) and in the open fractures 2·7 litres (range 1·0–4·4 litres). In 6 patients with closed fractures (e.g., patients 74, 102, 105, and 18) repeated estimations revealed an average blood-loss within 24 hours of 1·6 litres, a total loss of 2·3 litres; the average later loss was therefore 0·7 litre. Almost a third of the total blood-loss occurred after 24 hours, which is a much higher proportion than that found in most other injuries. In some patients the continued bleeding could be assessed from swelling of the thigh which increased for two or three days.

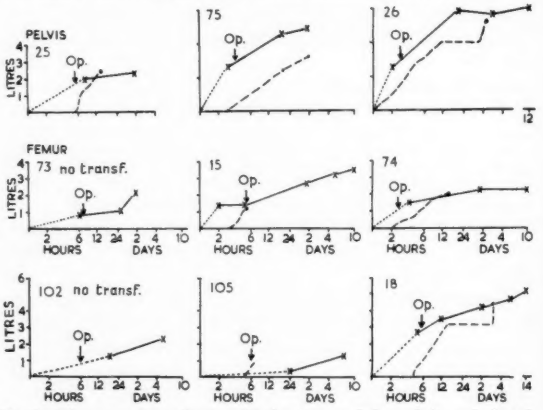

Fig. 2—The same in patients with fractures of the pelvis and closed fractures of the femur.

5 of the 12 patients with closed fractures were not transfused. Their total blood-loss averaged 1·6 litres (range 0·8–2·7 litres), compared with 1·9 litres (range 0·4–4·7 litres) in the transfused cases.

In 2 patients with supracondylar fractures (patients 73 and 15), as with the other fractures of the femur, a high proportion of the total loss occurred late. Fractures of the upper end of the femur gave variable results. These patients are usually elderly and the pre-accident "normal" blood-volume read off from tables may therefore be less accurate.

Fractures of Pelvis (fig. 2)

These injuries ranged from a comparatively minor fracture of the ilium (total loss 0·6 litre) to two severe crushing injuries of the pelvis with considerable soft-tissue damage, including large perineal wounds (5·8, and 6·0 litres [patient 26]). The total blood-loss in 7 patients averaged 3·6 litres, but 3 of these with the more usual type of injury lost about 2·5 litres. The total blood-loss in the 2 most severe cases exceeded their blood-volume. This is one of the few single injuries in which

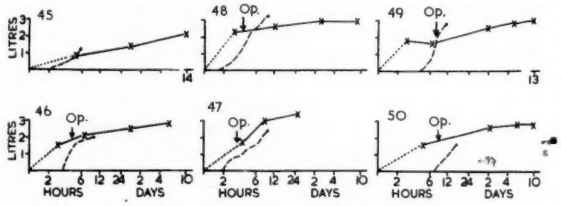

Fig. 3—The same in patients with crush injuries of the chest.

severe bleeding may be the cause of unexpected collapse. In 1 case the major blood-loss of 4·4 litres occurred between two and twenty hours after injury, while in 2 other patients half the blood-loss had taken place in the four hours after injury.

Abdominal Injuries

Most of these injuries were closed crushing injuries, but three stab wounds were included. Blood-loss was negligible when no viscera were involved, 3·4 litres in three hours when part of the mesentery and its vessels were torn, and 2·4 to 3·9 litres when kidney or spleen were completely ruptured. But a minor tear of even a highly vascular organ such as the spleen caused little bleeding (0·4 litre). On 5 patients repeated estimations showed an average blood-loss in three hours of 0·5 litre compared with an average total loss of 1·1 litres. In only 2 of these patients was the total loss over 1 litre. Swabs weighed at operation provided a valuable guide to the initial blood-loss.

Chest Injuries (*fig. 3*)

All patients had multiple fractures of ribs with some respiratory embarrassment. Cyanosis was present in only a few, and in these was transitory. No tracheotomies were performed, and the only death was due to an associated head injury.

Of these 12 patients, 8 had some associated injury. Total blood-loss after twenty-four hours averaged 2·5 litres; the majority had a loss within 0·5 litre of this figure (see table). It exceeded the loss expected from radiographic or clinical evidence of hæmothorax, and it is possible that much of the blood-loss came from damage to the chest wall itself. On 8 of these patients repeated estimations were performed (e.g., fig. 3), and in most approximately half the total blood-loss occurred in the first three to five hours. On average, the early loss was 1·6 litres, compared with a total loss of 2·8 litres.

Injuries to Head and Neck

Patients with head injuries were only rarely investigated. In the 3 studied, bleeding had become a major problem, either because it had been profuse at operation or because it had continued over a long period. In all the loss was considerable (2·9–5·5 litres).

Upper-limb Injuries (*fig. 4*)

The patients studied were selected because of their severe injuries.

3 had a laceration dividing an artery but causing little other soft-tissue damage (e.g., patients 32 and 34). Although controlled by tourniquet within an hour of injury, bleeding was brisk, with losses of 3·0 litres from the brachial artery, 2·4 litres from the ulnar artery, and 2·1 litres from the superficial palmar artery, at two to four hours after injury. The other patients, in whom soft-tissue damage was greater, also lost an appreciable amount, the total after twenty-four hours ranging from 1·9 to 5·4 litres (average 2·9 litres). In particular it may be noted that patients with a hand crushed by machinery and sustaining skin loss or amputation of fingers lost about 2 litres of blood (patients 36, 35, and 38). In 8 patients repeated estimations showed that the major loss occurred early. In 6 patients in whom estimations were performed at four to six hours (postoperatively) and after two days, the average early loss was 82% of the total (1·8 litres, compared with 2·2 litres).

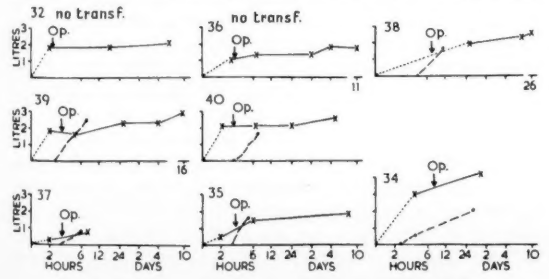

Fig. 4—The same in patients with upper limb injuries.

Multiple Injuries (*fig. 5*)

Sometimes the cumulative effect of comparatively minor injuries resulted in appreciable blood-loss (a patient who was given 3·2 litres, with fractures of the skull, malar bone, scapula, and ankle, and wounds of face and scalp lost in all 3·5 litres). In others the individual injuries were severe: for example, a patient (no. 60) with traumatic amputation of arm and leg, lost 5·4 litres.

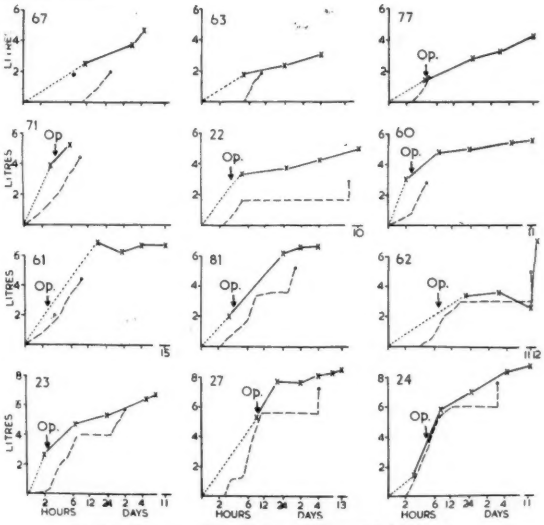

Fig. 5—The same in patients with multiple injuries.

It was sometimes possible to assess the loss fairly accurately from experience of individual injuries. In one case (patient 22) the fractured femur would be expected to cause a 1·5–2·0 litre loss, the fractured tibia 1·5–2·0 litres, the fractured radius and ulna about 0·5 litre, a total of about 4 litres. The actual blood-loss was 4·2 litres.

In 12 patients total blood-loss exceeded total circulating blood-volume. Only 2 of these patients died, both from a severe head injury. In 10 of the 12, the large blood-loss was caused by severe injury to thigh and/or pelvis, together with other injuries. In the other patients the cause was bleeding from the superior sagittal sinus, and arterial bleeding in the leg.

Estimations carried out on 12 patients within six hours of injury and repeated more than twenty-four hours later revealed an average early loss of 1·8 litres and a total blood-loss of 4·2 litres, suggesting that 43% was lost in the early period. These figures are rather heavily biased, however, by one case (patient 24). Without this one patient the corresponding figures are 1·9 litres for early and 3·8 litres for total loss, so that on average 50% of the total loss came in the first two to five hours after injury.

ERRORS IN BLOOD-LOSS MEASUREMENT

Results of blood-loss measurements were in general consistent with other evidence of blood-loss; but some

inconsistencies were found with the later hæmoglobin levels, and with clinical assessment of blood-loss from local swelling, external bleeding, and swab weighing. These might be due to a false assessment of the patient's pre-accident red-cell volume, or faults in its estimation. The results of 200 direct red-cell volume measurements, and 37 plasma-volume measurements in 85 patients on whom repeated estimations were performed have therefore been critically reviewed for these inconsistencies.

Possible Error in "Normal" Values

In adults a normal value of the red-cell volume, based on height, should be taken rather than the average normal for all adults.

In 1 patient (no. 23, fig. 5) with multiple injuries measurement of the blood-loss suggested a hæmorrhage greater than expected on the clinical evidence. The amount of blood transfused was greater than the clinical assessment but less than the blood-loss measurement. The hæmoglobin-level rose in the ensuing days, suggesting that the clinical assessment and not the blood-loss measurement had been correct. Nine months after injury this measurement was repeated and his red-cell volume was considerably less than the normal average for his height. If his pre-accident red-cell volume was the same as the volume at follow-up, the measurement after the injury overestimated the loss by $1^1/_2$ litres.

Smaller errors of 0·5–1 litre were suspected for similar reasons in 5 out of 85 patients. Usually they were detected through inconsistency with the later hæmoglobin-levels.

Possible Errors in Direct Red-cell Volume Measurement

In 1 patient (no. 62, fig. 5) with multiple injuries the estimation carried out on the eleventh day after injury revealed an unexplained increase of 1·0 litre. Within a few hours a major secondary hæmothorax had developed. The error may have been due to a wrong estimate of red-cell volume because of the state of the circulation. In another patient (no. 67, fig. 5) with multiple injuries and dying of a head injury the last red-cell volume estimate, on the fifth day after injury, differed by about 1 to $1^1/_2$ litres of blood from the clinical assessment. More hæmorrhage was not apparent at necropsy; and it is more likely that the red-cell volume estimate was at fault.

In a few patients there was an unexplained increase in red-cell volume, but only in 1 (patient 5, fig. 1) was the resulting error in blood-loss measurement as much as 0·5 litre: a second estimate in this patient, made seven hours after injury, did not agree with the figure obtained by weighing operation swabs and may well have been an overestimate.

In 4 patients repeated red-cell volume estimates showed a fall of red-cell volume between days ten and sixteen associated with a falling hæmoglobin, but with no clinical evidence of red-cell disappearance. This may have been due to a false low estimate of the circulating red-cell volume and hence about a 0·5 litre overestimate of blood-loss.

In 2 out of 85 patients the error in blood-loss measurement probably exceeded 1 litre.

Possible Errors in Plasma-volume Measurements

A similar approach was used in 35 patients whose red cell volume was measured by the plasma-volume/hæmatocrit method. In 1 patient (no. 24, fig. 5) with multiple injuries the blood lost was probably underestimated by 1–1·5 litres in the initial estimation; and in 6 of the remaining 34 patients there was a possible error of the order of 0·5 litre of blood.

Possible Contribution of an Abnormal Circulation to a False Red-cell-volume Estimate

A similar proportion of minor inconsistencies (2/40) was found in the 40 red-cell volumes estimated in the first six hours after injury. The 3 cases in which the difference exceeded 1 litre of blood were estimates made more than six hours after injury. In all there was some evidence of gross circulatory upset—e.g., a developing hæmothorax, a transfusion running in at the rate of 700 ml. in half an hour, or a moribund patient. In general, red-cell volume estimates were made when the circulation was relatively stable. In only 3 patients was a transfusion run at a rate exceeding 500 ml. per hour. The pulse-rate was over 120 per minute on 9 occasions, and the systolic blood-pressure was less than 100 mm. Hg on 6 occasions.

Discussion

Many surgeons find it hard to believe that injured patients lose as much blood as we have described. Occasionally an individual estimate may be wrong, but consistent results in repeated tests are probably correct.

Accuracy of Blood-loss Measurement

The greatest error arises from ignorance of the patient's pre-accident blood-volume. The likely error if height alone (Gibson and Evans 1937) or more complicated guides are relied on, has been adequately reviewed (Allen et al. 1956, Hicks et al. 1956, Muldowney 1957, Zak and Earle 1957, Wennesland et al. 1959). Errors of up to 1 litre of blood will be made from time to time.

The technical accuracy of the ^{32}P, ^{51}Cr, and T.1824 methods is now well defined in normal individuals. In our patients simultaneous estimations with ^{32}P and ^{51}Cr agreed well. The curves showing the rate of disappearance of the labelled material from the circulation, the proportion of radioactivity between red cells and "supernatant" and the body/venous hæmatocrit ratio all suggested that the patients were not significantly different from normal individuals (Davies and Topley 1959). Noble and Gregersen (1946) found delayed mixing times in "shock", but normal mixing times in the absence of "shock". With the few exceptions already described, all our patients had an apparently normal circulation.

Hæmorrhage alone seems responsible for the lowered red-cell volume (Evans et al. 1944a, Evans et al. 1944b, Emerson and Ebert 1945, Stewart and Warner 1945, Noble and Gregersen 1946, Grant and Reeve 1951, Prentice et al. 1954). But Gelin (1956) believes that hæmorrhage does not explain all the red-cell disappearance and presents a case for red-cell sequestration. If sequestration occurred in our patients, the cells were not returned to the circulation in sufficient quantity to increase the red-cell volume significantly during the serial estimations.

In repeated red-cell volume estimations red-cell volume frequently fell after hæmorrhage was assumed to have ceased. Falls of up to 15% have been measured in patients with little apparent blood-loss and confined to bed (Davies and Fisher 1958) possibly as a result of a physiological response to rest. Of total blood-loss measures 4 to 10 days after injury in immobilised patients, approximately 0·5 litre may therefore be due to factors other than hæmorrhage.

Clinical Assessment of Blood-loss

Clinical assessment of blood-loss may be extremely difficult. When there is a closed injury of one limb, and swelling can be compared with the normal side, the loss can be judged fairly accurately. The degree of swelling produced by known volumes of surgical felt wrapped round a limb can be a useful guide (Clarke, Topley, and Flear 1955). In addition, increasing swelling in the first twenty-four hours after injury is a good indication of continued bleeding.

When injuries are open it is more difficult. The quantity of blood lost on clothes and dressings is not easy to estimate; and there is an unknown loss at the accident site. Actually measuring external blood-loss by weighing swabs and clots, and fluid blood collected by suction can be invaluable. In abdominal injuries in which external indications are no guide, weighing swabs at operation

yields an assessment which is often sufficiently accurate to control transfusion. In these cases, of course, weighing swabs measures the blood which has been lost since the time of injury and not merely operative blood-loss. In most of our patients operative blood-loss contributed only a small proportion to the total. But, in patients in whom skin-grafting is carried out, or in whom extensive exploration is necessary, operative loss becomes significant and its accurate measurement definitely advantageous.

Many injuries remain in which neither limb-swelling nor weighing swabs can indicate the blood-loss. Grant and Reeve (1951) found it helpful to think of " hands " of injured tissue. If the damage was less than 1 hand, blood-loss was usually less than 10%; 1–3 hands, loss 20–40%; 3–5 hands, about 40%; over 5 hands, 50% or more. Noble and Gregersen (1946) related the extent of blood-loss to the number of major fractures. But each case must be assessed individually. The amount of damaged tissue, both visible and hidden (assessed by swelling and degree of displacement of fractures), and the vascularity of the tissue must be taken into account. It is well known that wounds of the face and scalp may bleed freely; in our series after crush injuries to the hand considerably more blood was lost than with comparable tissue damage elsewhere. We relied largely on past experience of similar cases in which blood-volume estimations had been performed. Only by actual blood-volume measurements on one's patients, or by checking the adequacy of transfusion replacement by serial hæmoglobin measurements four to fourteen days later, can " past experience " be built up.

Time of Blood-loss

It is often mistakenly believed that by the end of an operation blood-loss has virtually ceased. Sometimes later loss is obvious, as at the donor site after skin-grafting, when blood-soaked dressings demonstrate the extent of postoperative bleeding. In most patients serial blood-volume estimations have shown that there is a small abating loss postoperatively. The greater the amount of damaged tissue remaining, the more significant is this later loss likely to be. For this reason a major injury with amputation may actually cause less blood-loss than a serious but less severe injury after which the limb is saved (compare 2 patients in whom the six-hour loss was 4·7 and 5·9 litres, but the total loss 5·4 and 8·4 litres respectively).

Severe civilian injuries are usually brought quickly to hospital—most of our patients within an hour—and it is during the first hour or two in hospital that one wishes to estimate transfusion requirements. We performed the first blood-volume estimation on our patients two to five hours after injury; *on average* 50% of the total blood-loss had occurred by then. But this was true only when operative blood-loss was not great and postoperative loss was a small diminishing bleed. The chief exceptions to this were fractures of the femur and injuries to the upper limb. In the former we have an inadequate number of observations to time the early loss; but the loss after 24 hours was probably greater than in other injuries. Few of these cases had open operation to secure hæmostasis or fixation of the fracture; and postoperatively a considerable volume of damaged tissue would remain. The reverse was true for injuries of the upper limb. In these, hæmostasis was secured at operation and much of the damaged tissue removed. Early blood-loss then formed a higher proportion of the total. It is important, however, to assess each case individually for signs of continued bleeding, such as blood-soaked dressings or increasing swelling of limbs, rather than to rely on generalisations.

Effect of Transfusion on Blood-loss

In the presence of hypotension blood-loss will be less than with a normal blood-pressure. In so far as blood-transfusion restores or maintains the blood-pressure, it will increase blood-loss. Because of the risks of vascular collapse, and renal and cerebral damage, hypotension for more than a brief period should clearly be avoided while post-traumatic hæmorrhage continues. The additional loss that transfusion often causes is therefore necessary to render operation and survival possible.

Within the range of safety, there is no clear evidence that the rate and amount of blood transfused significantly influences the amount of hæmorrhage. These conclusions are based on the results described for different injuries, especially closed fractures of the femur. These results can be used to compare transfused patients with those not transfused; but the comparison is unsatisfactory because it is often the less severely injured patient who does not require transfusion. Limited supporting evidence comes from a controlled trial of different levels of transfusion replacement (Topley and Fisher 1956).

Significance in Treatment

The evidence we have presented is designed to assist in a more precise assessment of blood-loss, rather than to evaluate how far it should be replaced. For many injuries full replacement gave good results, but those losing less than one litre may benefit little from transfusion. In a controlled trial of different levels of transfusion replacement (Topley and Fisher 1956), it was extremely difficult, even with serial blood-volume estimations, to maintain a desired level with greater accuracy than $\pm 10\%$. Without these measurements it is even more difficult. Whatever replacement is considered desirable, it is essential that the extent of the loss be known, and the difficulties in maintaining the level appreciated.

The amount of blood a patient with a particular injury will lose should be assessed as soon as possible—not only the blood already lost but also the blood which will be lost. The actual rate of transfusion and final total can be adjusted depending on further bleeding and response to treatment. By maintaining a normal circulation and good general condition it is then possible to carry out planned, definitive surgery early, and shorten the period of illness and incapacity.

Summary

Blood-loss was measured in 140 patients with various injuries. Repeated blood-volume estimations were carried out on 75 of these patients to time the blood-loss. *On average*, 50% of the total loss occurred in the first two to five hours after injury.

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INTRAVENOUS ALBUMIN IN THE TREATMENT OF DIURETIC-RESISTANT ASCITES IN PORTAL CIRRHOSIS

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INABILITY of the diseased liver to maintain the normal concentration of albumin in the plasma is an important influence in causing fluid retention in the form of œdema and ascites. In the absence of effective means of promoting albumin synthesis by the liver, albumin has been infused intravenously in the treatment of œdema and ascites (Janeway et al. 1944, Faloon et al. 1949, Post et al. 1951). Although the difficulty of preparing salt-poor human serum albumin has restricted the application of this form of treatment, it is now established that the serum-albumin and serum colloid-osmotic pressure (C.O.P.) can be restored to normal and maintained there by repeated albumin infusions (Post et al. 1951, Dykes 1960). The clinical result of elevation of serum-albumin is often diuresis with loss of œdema and ascites; this occurred in 11 of 20 patients in Faloon et al.'s series and in 21 of the 34 patients treated by Post et al.

The factors which determine the clinical response to intravenous albumin therapy are obscure since restoration of the serum-albumin level to normal does not necessarily cause regression of ascites. Albumin infusions may accelerate ascites formation (Watson and Greenberg 1949), and it seems possible that this is due to a further elevation of portal venous pressure accompanying the increase in plasma-volume which has been shown to occur (Patek et al. 1948). The precipitation of bleeding from œsophageal varices noted by Faloon et al. (1949), Havens and Bluemle (1950), and Post et al. (1951) would be in keeping with this view.

The purpose of the present investigation was to assess the clinical effects of intravenous albumin therapy in patients with portal cirrhosis and to correlate these with changes in the colloid osmotic and hydrostatic equilibrium in the splanchnic area.

Methods and Patients Studied

The effect of a course of intravenous infusions of albumin was studied eleven times in 10 patients, each of whom had portal cirrhosis and was accumulating ascites before treatment was started. In 1 patient the liver lesion apparently resulted from progressive hepatitis which had started eighteen months previously; in the other 9 the ætiology was unknown. None gave a history of alcoholism. The duration of ascites varied from three months to eight years, and 6 patients also had œdema of the lower extremities at the time of study. Of the 10 patients 9 had recently been found to be resistant to treatment with diuretics and dietary sodium restriction, while the 10th had had no previous treatment.

All patients were admitted to hospital for the duration of the investigation and received a diet containing approximately 22 mEq. of sodium daily. Daily weighing and measurements of the fluid intake and output were used to assess the rate of gain or loss of ascites and œdema.

After a control period of at least five days, intrasplenic pressure (which was used as an index of portal venous pressure [Atkinson and Sherlock 1954]), ascitic-fluid pressure, and hæmatocrit were measured, and samples of blood and ascitic fluid were taken for protein and C.O.P. measurements. These measurements were repeated on the day after the completion of a course of intravenous infusions of salt-poor human albumin, in a dosage of 50 g. in a litre of pyrogen-free water, on alternate days to a total of 150–300 g. In 4 patients who failed to respond to this treatment the effect of a further course of diuretic (hydroflumethiazide in cases 1, 7, and 9, and bendrofluazide in case 10) was observed.

Intrasplenic and ascitic-fluid pressures were measured by methods previously described (Atkinson 1959).

Colloid osmotic pressures were measured by the electronic colloid osmometer described by Rowe and Abrams (1957). Potassium oxalate was used as anticoagulant, in a concentration of approximately 2 mg. per ml. of blood. Plasma C.O.P. by this method in 67 normal subjects averaged 36·3 cm. of water (standard deviation ±3·61), while slightly higher values were obtained using serum or heparinised plasma (mean 38·7 cm. ±3·15) (Losowsky et al. 1961).

Results

Clinical Observations (table I)

During the control spell in each of the eleven periods of study the patient accumulated ascites, shown by a steady increase in body-weight. Intravenous albumin therapy reversed this trend in seven of the eleven periods of study; the weight decreased, diuresis occurred, ascites diminished and œdema when present disappeared.

Of the 7 patients who showed a satisfactory clinical response, 2 died of progressive liver-cell failure four weeks and five weeks after the completion of albumin therapy. In each ascites reaccumulated terminally. The other 5 patients were discharged from hospital six to sixteen days after albumin therapy. Since albumin was not available for maintenance therapy diuretics were restarted in each of these five patients before discharge from hospital, and supervision was continued in the outpatient clinic. In 3 of these patients ascites reaccumulated three, four, and four months after completion of albumin infusions, and 1 of them was given a further course of albumin infusions six months later, this time without benefit (vide infra). The two remaining patients have as yet shown no tendency to reaccumulate fluid fifteen months and six months after albumin therapy.

Ascites continued to increase during the course of albumin infusions in 4 patients (including 1 who had responded to a previous course). The rate of accumulation of fluid appeared to be accelerated during the period of albumin therapy in two of these patients, while in the other 2 the rate of gain of weight was unaffected. Diuretic therapy was restarted shortly after the completion of the albumin infusions in all 4 of these patients. In 2, both previously resistant to diuretics, diuresis was induced, and in 1 ascites has now been controlled by this means

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TABLE I—CLINICAL DATA

Case no.	Age (yr.)	Sex	Duration of ascites (yr.)	Œdema	Total dosage of albumin (g.)	Effect on ascites	Duration of remission (mos.)	Subsequent course
1	66	F	1	Slight	300	Decreased	4	Controlled by diuretics
2	47	F	1	Gross	300	,,	2	Died in liver failure
3	63	M	2	,,	200	,,	15+	Ascites controlled without diuretics
4	58	F	8/12	,,	300	,,	6+	do.
5	49	F	8	Nil	150	,,	1	Died in liver failure
6	59	M	?	Moderate	200	,,	4	do.
7	26	F	1	Nil	300	,,	3	Ascites reaccumulated despite diuretics
,,	,,	,,	1 1/2	,,	250	Increased	—	Responded to diuretics
8	70	F	1 1/2	,,	200	,,	—	Died in liver failure
9	60	F	6/12	,,	300	,,	—	do.
10	64	F	3 1/2	Moderate	200	,,	—	Responded to diuretics and ascites controlled for 7 mos.

for six months. Neither of the other 2 patients responded at all to renewed diuretic therapy, both required further paracentesis, and each died within four weeks of albumin treatment.

Side-effects

Although œsophageal varices had been demonstrated in 9 of the 10 patients, bleeding was not encountered during the period of study in any of our patients. 2 became breathless during infusion, and pulmonary œdema was suspected. This symptom was not severe enough to necessitate any measures other than slowing the rate of infusion.

In 3 cases transient shivering developed during one or more infusions. This usually appeared to be due to the albumin having been incompletely dissolved. On one occasion, however, after the patient had had rigors and pyrexia during an infusion, a staphylococcus was cultured from the albumin solution remaining in the bottle. This was ascribed to faulty aseptic technique in dissolving the albumin, and the staff was thereafter instructed to discard the bottle if in any doubt about possible contamination. The patient had no further symptoms after this episode.

Plasma and Ascitic-fluid Protein Levels (table II)

Pre-treatment plasma-albumin levels ranged from 1·4 to 4·7 (mean 2·6) g. per 100 ml., rising to levels of 2·8 to 4·7 (mean 3·8) g. per 100 ml. after treatment. 1 patient showed no change in plasma-albumin level, but in the others it rose by 0·8 to 2·3 g. per 100 ml. The magnitude of the increase in plasma-albumin level in those patients who responded to treatment did not differ significantly from that in those who did not respond, the mean increases being 1·3 and 1·0 respectively (S.E. of difference 0·35; $0·4 > P > 0·3$); the final concentration in all the patients who failed to respond was within the range in those who responded.

Measurements of ascitic-fluid albumin concentration before and after nine of the periods of albumin therapy showed a rise which roughly paralleled the increase in plasma level.

This was not so in the 1 patient who had no increase in plasma-albumin after albumin infusions, but her ascitic-fluid albumin increased from 1·5 to 1·9 g. per 100 ml. Paracentesis abdominis subsequently yielded 17 litres of fluid. Since she had gained 5·9 kg. in weight during the period of treatment and had no œdema, we estimated that some 6 litres of ascites had accumulated. The increase in ascitic fluid albumin would thus account for approximately three-quarters of the 200 g. of albumin administered.

Plasma and Ascitic-fluid Colloid Osmotic Pressures (table II)

Plasma-C.O.P. before treatment was subnormal in nearly all patients, ranging from 16·5 to 30·3 (mean 24·6) cm. H_2O. All patients showed a rise in plasma-C.O.P. after treatment, the range then being 22·0–36·6 (mean 29·4) cm. H_2O (fig. 1).

TABLE II—PLASMA AND ASCITIC-FLUID PROTEIN AND C.O.P. LEVELS

Case no.	Pre- or Post-albumin therapy	Plasma			Ascitic fluid			Colloid osmotic gradient (cm. H_2O)*	Intrasplenic pressure (cm. H_2O)	Ascitic-fluid pressure (cm. H_2O)	Hæmatocrit
		Albumin (g. per 100 ml.)	Globulin (g. per 100 ml.)	Colloid osmotic pressure (cm. H_2O)	Albumin (g. per 100 ml.)	Globulin (g. per 100 ml.)	Colloid osmotic pressure (cm. H_2O)				
1	Pre	2·7	2·9	24·2	1·1	1·1	6·0	18·2	29	11	37·5
	Post	3·5	3·3	33·6	1·7	1·6	12·3	21·3	22		36
2	Pre	1·8	2·8	19·7	0·3	0·5	3·5	16·2	30	14	36
	Post	2·8	2·8	22·1	0·7	0·7	6·1	16·0	22		
3	Pre	2·7	3·3	20·8					29		36
	Post	3·9	2·9	30·3					28		36
4	Pre	2·5	2·0	19·1	0·5	0·5	2·5	16·6	31	16	43
	Post	4·7	1·5	28·0	1·5	0·9	7·7	20·3	32	7	32
5	Pre	2·2	3·0	16·5	0·5	0·4	1·8	14·7	30	9	
	Post	3·5	2·4	22·0	1·7	0·9	7·2	14·8	27		
6	Pre	3·1	1·9	27·8	0·4	0·1	1·7	26·1	44	16	36
	Post	4·2	1·6	30·7		No ascites			43		
7a	Pre	2·5	4·6	24·7	0·8	0·9	4·6	20·1	46	16	36
	Post	4·2	3·9	36·6	2·0	1·2	10·9	25·7	51	10	32
7b	Pre	2·5	3·5	25·8	0·5	1·5	5·2	20·6	52	25	
	Post	3·7	3·2	29·7	1·2	1·3	7·4	22·3	62	23	
8	Pre	3·6	3·2	31·4	1·5	1·0	7·7	23·7	46	20	25
	Post	3·6	2·6	32·6	1·9	1·1	12·5	20·1	48	24	
9	Pre	1·4	4·4	21·5	0·8	0·8	3·9	17·6	36	12	35·5
	Post	3·1	2·9	35·3	1·4	1·2	7·3	28·0	47	20	29
10	Pre	3·2	2·8	30·3	1·4	1·5	11·3	19·0	39	12	21
	Post	4·2	2·0	33·1	2·9	1·1	14·4	18·7	46	19	18·5

* Plasma colloid-osmotic pressure minus ascitic colloid-osmotic pressure.

Although the mean rise was greater in the patients who responded, the final level reached did not differ significantly between the two groups, since the initial values were, in general, higher in the patients who did not respond. These findings provide further confirmation that there is no single critical level of plasma C.O.P. for ascites formation.

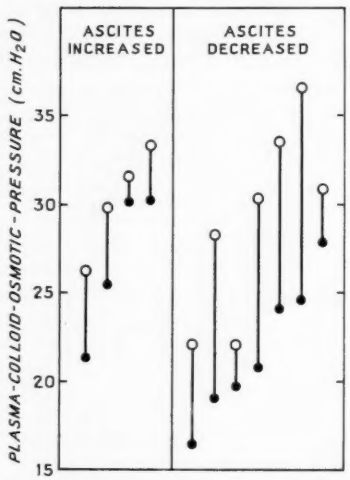

Fig. 1—Changes in plasma colloid-osmotic pressure with intravenous albumin therapy.

The values before treatment are shown as closed circles and those after as open circles. There is no critical level at which ascites formation ceases.

Ascitic-fluid C.O.P. was measured before and after albumin infusions in 9 patients. Pre-treatment levels varied from 1·7 to 11·3 (mean 4·4) cm. H_2O and rose to 6·1 to 14·4 (mean 8·6) cm. H_2O. In general the increase in ascitic-fluid C.O.P. was proportional to the rise in plasma-C.O.P. (fig. 2). Although in 1 patient, who rapidly gained ascites during treatment, the ascitic-fluid C.O.P. increased by a much greater proportion than did the plasma-C.O.P., the group who gained ascites did not as a whole show a disproportionate rise of ascitic-fluid C.O.P. to suggest that increased leakage of albumin into the peritoneum was the cause of the failure to respond.

Since ascitic-fluid C.O.P. rose after albumin therapy, the mean increase in the C.O.P. gradient between plasma and ascites was much smaller than the mean rise in plasma-C.O.P. and only amounted to about a third of the mean rise in this value. The greatest increase in this gradient (10·4 cm. H_2O) occurred in case 9, who continued to accumulate ascites; in the other patients, in many of whom ascites diminished, the gradient did not increase by more than 6 cm. H_2O. Hence the clinical response to albumin therapy could not be explained simply by an alteration of the C.O.P. gradient between plasma and ascitic fluid.

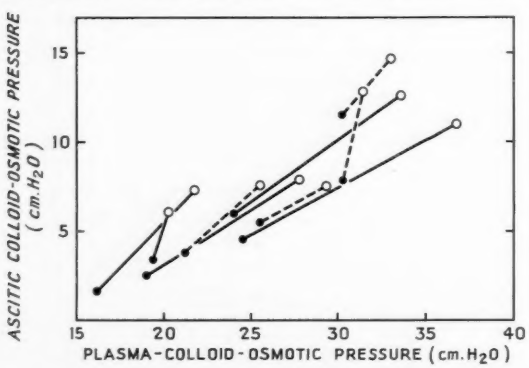

Fig. 2—Changes in plasma and ascitic-fluid colloid-osmotic pressure (C.O.P.) with intravenous albumin therapy.

The values before treatment are shown as closed circles and those after as open circles. Cases in which ascites decreased are shown as continuous lines and those in which it did not as broken lines. In general the rise in ascitic-fluid C.O.P. is related to, but somewhat smaller than, the rise in plasma-C.O.P. With 1 possible exception unduly rapid leakage of albumin into the ascitic fluid did not account for failure to respond to treatment.

Intrasplenic Pressure (fig. 3)

Measurements of intrasplenic pressure before albumin therapy showed that it was significantly greater in the group which did not respond than in that which did, the mean levels being 43 and 34 cm. H_2O respectively (S.E. of difference 3·99; $P < 0·05$).

Intravenous albumin therapy resulted in an increase in intrasplenic pressure in each of the 4 patients in whom ascites did not diminish, and the post-treatment pressures in this group lay between 46 and 62 cm. H_2O. In contrast intrasplenic pressure fell in 5 of the 7 patients who responded to albumin therapy. Hence the difference between the intrasplenic pressures of the two groups of patients was even more striking after treatment than it was initially. The mean post-treatment intrasplenic pressure was 32 cm. H_2O in the group which responded, compared to 51 cm. H_2O in the group in which ascites increased (S.E. of difference 4·65; $P < 0·01$). In general the effect of treatment was related to the pre-treatment level of intrasplenic pressure; the higher this pressure, the more likely it was to increase further after albumin therapy. In the 6 patients who still had sufficient ascites for ascitic-fluid hydrostatic pressure measurements to be repeated after albumin therapy, the changes observed ranged from a fall of 9 cm. to a rise of 8 cm. H_2O. In all of these 6 patients intrasplenic pressure had risen; yet in 3 ascitic-fluid hydrostatic pressure fell, suggesting that alteration in intra-abdominal tension did not account for the increases in intrasplenic pressure.

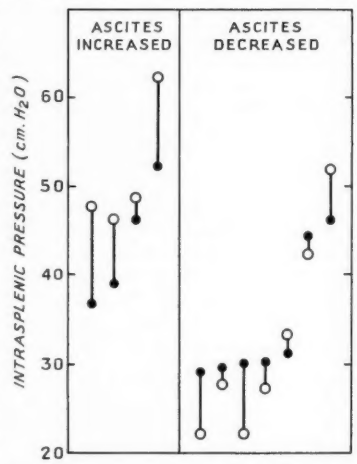

Fig. 3—Changes in intrasplenic pressure with intravenous albumin therapy.

The values before treatment are shown as closed circles and those after as open circles. Intrasplenic pressure was in general higher initially and rose further after therapy in cases which did not respond.

Hæmatocrit

The hæmatocrit values generally fell over the period of treatment, which would be in keeping with increase in plasma-volume occurring as a result of albumin therapy.

Threshold Values of Plasma Colloid-Osmotic Pressure and Intrasplenic Pressure for Ascites Formation

It has previously been shown that, in patients with liver disease, consideration of serum-albumin and intrasplenic pressure together enables cases in which ascites is being formed to be clearly distinguished from cases in which it is not being formed (Atkinson and Losowsky

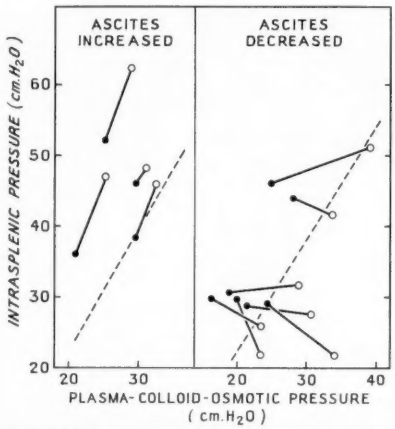

Fig. 4—Intrasplenic pressure shown in relationship to plasma colloid-osmotic pressure before (closed circles) and after (open circles) albumin therapy.

The ascites threshold, shown by the broken line, gave a good delineation between the post-therapy values of patients who did not respond (and remained above the line—i.e., on the ascitic side) and those of patients who responded (and lay below the line—i.e., on the non-ascitic side).

1961). As might be expected, a similar relationship exists when plasma-C.O.P. is substituted for plasma-albumin; when intrasplenic pressure is plotted against C.O.P. a straight line can be drawn separating cases in which ascites is being formed from those in which it is not being formed. This line representing the ascites threshold is shown in fig. 4. Before treatment all patients were accumulating ascites, and the points obtained when intrasplenic pressure was plotted against plasma-C.O.P. all lay on or above the threshold line. After treatment the values fell on the opposite side of the threshold in each of the 7 patients who responded by losing ascites. In contrast the point after treatment often moved further from the threshold line in the group in which ascites increased. This was due to the increase in intrasplenic pressure, which more than counter-balanced the increase in plasma-C.O.P.

Discussion

Our findings suggest that intravenous albumin therapy may be of value in the management of ascites in portal cirrhosis when diuretics are ineffective. Furthermore the response to diuretics may be restored by intravenous albumin, as in 2 of our patients. We used rather low total dosages of albumin compared with those used by others (Post et al. 1951); and possibly had larger quantities been given the proportion of patients responding would have been higher. On the other hand, this might well have caused severe pulmonary œdema or bleeding from varices, neither of which was encountered.

We have confirmed that the increase in plasma-albumin concentration or plasma-C.O.P. is not the sole factor determining the response to intravenous albumin therapy. Albumin infusions expand plasma-volume; and we have shown that the magnitude of any associated increase in splanchnic capillary pressure, assessed from changes in intrasplenic pressure, is of great importance in determining the clinical response to this treatment. If large, this rise in splanchnic capillary pressure may more than counterbalance any rise in plasma-C.O.P. resulting from the albumin infusion, and the rate of ascites formation may then be actually accelerated. Patients with cirrhosis are unable to excrete intravenously administered saline solution normally and also show a defect in free water clearance (Schedl and Bartter 1960). Since the change in plasma-volume will be influenced by the volume and electrolyte content of the carrier solution for the albumin, it is conceivable that better results would be obtained if a more concentrated solution were used.

Measurements of plasma C.O.P. or protein levels and intrasplenic pressure are of much assistance in the choice of treatment for ascites in liver disease. Albumin infusions are of greatest value in patients with a low plasma-C.O.P. in whom ascites has developed with only moderate portal hypertension; while in those with a high intrasplenic pressure, by expanding plasma-volume, they are particularly liable to increase this pressure further and so accelerate ascites formation. Diuretics, which lower plasma-volume and so reduce intrasplenic pressure (Atkinson 1959), would seem the treatment of choice in patients with gross portal hypertension. If need be they may be supplemented by aldosterone antagonists, which increase their effectiveness in resistant ascites (Shaldon et al. 1960). This regimen may be strikingly effective in relieving ascites but carries a risk of inducing deterioration in liver function, probably because in these patients the reduction in plasma-volume necessary to relieve portal hypertension may be sufficient to impair hepatic blood-flow. Since the amount of portal blood perfusing the liver is often small in these patients (Iber et al. 1960), portocaval anastomosis sometimes offers a way out of this quandary when portal hypertension appears to be the dominant factor in causing ascites in cases where the plasma albumin or C.O.P. is only moderately depressed.

Summary

10 patients with portal cirrhosis and ascites, which in 9 was resistant to diuretics and dietary sodium restriction, were treated with intravenous salt-poor human albumin. In eleven periods of treatment ascites was controlled on seven occasions but increased on four. In two of the cases in which ascites increased, this responded to diuretics after albumin therapy.

Intravenous albumin caused an increase in plasma colloid-osmotic pressure, but on six occasions intrasplenic pressure also rose. The rise in intrasplenic pressure, which was greatest in those patients with the highest initial pressures, offset the effect of the increase in plasma colloid-osmotic pressure in those patients in whom ascites increased.

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INTESTINAL OBSTRUCTION COMPLICATING ANTICOAGULANT THERAPY *

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THE commonest complication of anticoagulant therapy is hæmorrhage. Numerous reports describe the frequency and nature of this side-effect; but, apart from gastro-intestinal bleeding in the form of hæmatemesis and melæna, there have been few references to other complications of this treatment. In 30 series, comprising over six thousand patients who have had short and long courses of anticoagulants, there is no mention of the condition to be described here. Nevertheless, in the past 5 years we have encountered seven patients with a clinical picture of subacute intestinal obstruction associated with excessive hypoprothrombinæmia due to oral anticoagulant therapy.

Berman and Mainella (1952) reported five patients with toxic effects of anticoagulants, one of whom developed abdominal pain, distension, tenderness, and vomiting. A plain radiograph of the abdomen revealed distension of the small bowel. At operation there was a hæmatoma (10 in. long) in the jejunal wall, and free blood in the peritoneal cavity. After resection of the hæmatoma the patient recovered. A similar case has been described by Pearson and MacKenzie (1958).

Describing the hæmorrhagic complications in fifty-three patients taking anticoagulants for cerebrovascular disease, McDevitt et al. (1959) mentioned a patient with intestinal obstruction due to a hæmatoma in the wall of the jejunum.

Mendelsohn and Iglauer (1953) reported two patients with abdominal symptoms associated with free blood in the peritoneal cavity. Plain radiographs of the abdomen showed distended loops of bowel in both cases; in one the entire serosa of the small bowel was hæmorrhagic, and in the other the condition, diagnosed by aspiration of the cul-de-sac, recovered without special treatment.

Perez-Mesa (1960) has recently reported two cases of paralytic ileus associated with long-continued dicoumarol therapy. Both patients recovered after resection of hæmorrhagic segments.

The Patients

Unless specific contraindications exist, we give anticoagulants routinely to all patients with acute myocardial infarction or with symptoms of impending infarction, and long-term anticoagulant therapy is given in cases with a history of two or more thromboembolic episodes. Treatment is usually started in hospital, and after discharge patients on long-term therapy are supervised as out-patients. At first, prothrombin-activity is determined daily, but after the maintenance dose of anticoagulant has been established, determinations are performed weekly or fortnightly. The prothrombin-activity is estimated by the one-stage method of Quick, the normal control value being 12–15 seconds. The upper and lower limits of the therapeutic range are considered to be 25 and 50 seconds (35% and 17%) respectively.

When these abdominal complications were encountered about a hundred of our patients were on long-term treatment. This incidence of major hæmorrhagic complications is not excessive because, among a hundred patients with impending infarction treated with anticoagulants for up to 8 years, 10% had major hæmorrhage (Beamish and Storrie 1960). This is the same figure as was reported by Owren (1957) among nearly three hundred patients treated for up to 11 years, and somewhat less than the 13% reported by Keyes et al. (1956) and McDevitt et al. (1959). In a hundred short-term courses of anticoagulant treatment given to eighty-nine patients, the only bleeding noted was macroscopic hæmaturia in three patients (Beamish and Carter 1956). Of the seven patients showing intestinal obstruction, three were having short-term (1 month or less) and four were having long-term (3 months or more) therapy.

Essential features of all seven patients are shown in the table. There were five males and two females, whose ages varied from 57 to 76 years, with a mean of 63 years. Phenindione (' Danilone ') was used in three cases, dicoumarol in two, and nicoumalone (' Sintrom ') and ethyl biscoumacetate (' Tromexan ') each in one case. Patients were treated for 3 weeks to 11 months, with an average of 18 weeks before symptoms began. The symptoms lasted 5 to 14 days, averaging 10 days, before admission to hospital. Total duration of the abdominal symptoms varied from 9 to 34 days, with a mean of 17 days.

The anticoagulant was stopped in all cases until prothrombin-activity reached the usual therapeutic level. In four patients the drug was then resumed; three patients had no further anticoagulant treatment. Neither vitamin K_1 nor blood-transfusion was required for any patient.

Long-tube intestinal decompression was used in five patients, but was not needed in the other two. All the patients recovered without recourse to surgery.

Illustrative Case-histories

Case 1.—A man, aged 58, who had had several episodes of myocardial infarction over 12 years, had been having dicoumarol therapy for 9 months before the present illness.

On admission to hospital he complained of intermittent colicky lower-abdominal pain and intermittent hæmaturia for the previous 3 weeks. He had begun to vomit 3 days before, and had noticed ecchymoses principally on his thighs two days before. He had been constipated for 2 days.

The abdomen was distended and resonant. Bowel sounds were present. The urine was loaded with red blood-cells. The prothrombin-time was 65·5 seconds (12% of normal). Temperature, pulse-rate, respiration-rate, and rectal examination were normal.

* A paper presented to the 12th annual meeting of the Canadian Heart Association, Montreal, P.Q., on June 6, 1959.

SUMMARY OF CLINICAL DATA

Case no.	Sex	Age (yr.)	Anticoagulant and length of therapy	Duration of abdominal symptoms (days)		Treatment
				Before admission	Total	
1	M	58	Dicoumarol; 9 mos.	14	34	Miller-Abbott tube
2	M	65	Nicoumalone; 11 mos.	12	18	Miller-Abbott tube
3	F	76	Dicoumarol; 4 wks.	14	19	Cantor tube
4	M	61	Phenindione; 6 mos.	14	19	Expectant
5	M	57	Phenindione; 3½ wks.	6	9	Miller-Abbott tube
6	M	59	Phenindione; 3 wks.	8	12	Miller-Abbott tube
7	F	66	Ethyl biscoumacetate; 3 mos.	5	12	Expectant

Fig. 1—Plain X-ray of the abdomen in case 1, showing fluid levels.

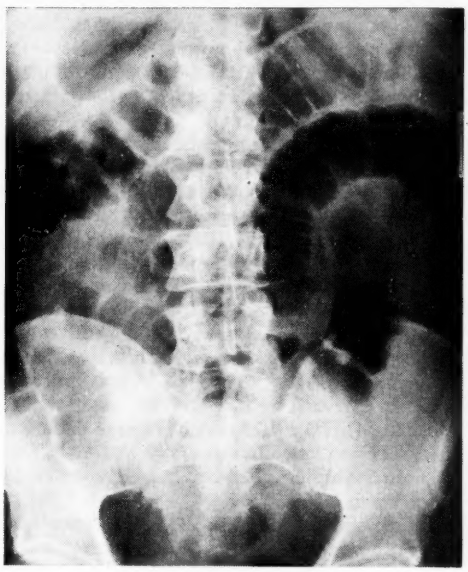

Fig. 2—Plain X-ray of abdomen in case 2.

Plain X-rays of the abdomen were consistent with small-bowel obstruction (fig. 1). A barium-enema showed a local segment of distended transverse colon and numerous diverticula.

Dicoumarol therapy was stopped, and continuous suction was applied via a Miller-Abbott tube. Fluids were given intravenously by continuous drip. 3 days later the patient passed flatus and had a small bowel movement. 11 days after admission X-rays still showed much small-bowel distension, with multiple fluid levels. Nevertheless he made good progress from this time onwards, and 22 days after admission there was no evidence, clinical or radiological, of intestinal obstruction.

Case 2.—A man, aged 65, who had previously had an anteroseptal infarction and a popliteal-artery thrombosis, had been having an anticoagulant, nicoumalone, because of impending infarction, for 11 months.

He had had colicky abdominal pains and hæmorrhagic blisters on the feet and ankles for 14 days before admission to hospital. For about 12 days he had noticed increasing abdominal distension, and for 10 days he had had mild diarrhœa with a small amount of bright blood in the stools. For the previous 3 days he had complained of intense nausea, and he had vomited several times.

His abdomen was distended and resonant, and the bowel sounds were slightly increased. The X-ray appearance was that of small-bowel obstruction (fig. 2). The prothrombin-activity was 25% of normal, although the dose of anticoagulant had been greatly reduced 2 days before admission.

A therapeutic level of prothrombin-activity was maintained using phenindione ('Danilone') as anticoagulant, and the small bowel was decompressed with a Miller-Abbott tube. On the 6th day in hospital the abdomen was soft, and he passed a normal stool.

Fig. 3—Small bowel showing multiple intramural hæmatomas and one in the root of the mesentery.

Discussion

The syndrome of subacute intestinal obstruction associated with excessive hypoprothrombinæmia should be readily recognised. The symptoms are of gradual onset, and the condition should be suspected when a patient taking an anticoagulant complains for several days of increasing abdominal pains and distension. Other visible hæmorrhagic manifestations—e.g., ecchymoses or hæmaturia—are commonly, but not necessarily, present.

Clinical suspension should be followed by immediate estimation of the prothrombin-activity (which was prolonged in all our cases), and by a plain X-ray of the abdomen. If the prothrombin-activity is within the therapeutic range a careful search should be made for some other cause of obstruction. Abdominal distension is quite commonly associated with painful renal lesions with or without hæmaturia, and also with hæmorrhage into the gut or peritoneal cavity; but the onset in such cases is acute.

In our cases mechanical obstruction

was suggested by the slow "crescendo" onset of colicky abdominal pain, with increasing abdominal distension, vomiting, constipation, and normal or increased bowel sounds. The symptoms and X-ray signs of intestinal obstruction persisted for several days after the prothrombin activity had returned to normal.

Three cases have been described of a single hæmatoma in the bowel wall due to anticoagulants (Berman and Mainella 1952, Pearson and MacKenzie 1958, McDevitt et al. 1959). The clinical features and progress of our patients suggest that hæmorrhage into the bowel wall, producing one or more hæmatomas, was the basis of the subacute intestinal obstruction. This would explain the gradual increase of symptoms as the hæmatoma increased in size, and the gradual decrease of symptoms with resolution of the lesion. One patient with this syndrome, not described in this series, was found at necropsy to have more than twelve such hæmatomas and one in the root of the mesentery (fig. 3). The administration of anticoagulants had been continued in this case for several days after the abdominal symptoms had become fairly severe. Death was due to cerebral hæmorrhage.

The most important point in the management of these cases is to restore the prothrombin-time to the therapeutic level, or to normal if in the opinion of the clinician the anticoagulant therapy may be discontinued. All our patients recovered with conservative management of the obstruction.

Summary

Attention is drawn to subacute intestinal obstruction arising during anticoagulant therapy in seven patients with excessive hypoprothrombinæmia.

The obstruction seemed to be due to hæmorrhage into the bowel wall, with hæmatoma formation.

Early recognition, restoration of the prothrombin-activity to a safe level, and conservative management of the obstruction led to recovery in all cases.

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ACTION OF STEROID THERAPY IN JAUNDICE

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THE place of cortisone and corticotrophin in the treatment of infective hepatitis has been much discussed. Often their use is followed by dramatic clinical improvement and a prompt fall in serum-bilirubin. The reason for this fall is by no means clear. Moreover the response is very variable, and a similar effect may occur in extrahepatic obstructive jaundice.

The simplest explanation for the response in hepatitis would be that cortisone, by its anti-inflamatory action, decreases cellular exudate and œdema in the liver and thus increases the secretion of bile. No detailed studies of bile-pigment excretion during steroid therapy have been reported, though in 1 patient with cholangiolitic hepatitis (Chalmers et al. 1955) the serum-bilirubin fell from 12 to 6 mg. per 100 ml. in four days without any rise in fæcal or urinary urobilinogen. On the other hand Summerskill and Avery Jones (1958) noted concomitant decreases in alkaline phosphatase, suggesting increased biliary excretion; and Ducci et al. (1957) also concluded that this was the main effect of steroid therapy. Experimentally there is some evidence (Chandler et al. 1957) that in dogs cortisone stimulates biliary excretion. In man Patterson et al. (1954) reported an increase in biliary flow in normal subjects given cortisone, although this finding has been disputed by later workers (Shay and Sun 1957, Clifton et al. 1958).

The response in obstructive jaundice is more difficult to explain. Katz et al. (1957) found a fall in serum-bilirubin of the order of 20–30% of the initial level despite complete absence of bile pigments from the stools. Other workers (Chalmers et al. 1956), however, have described a similar fall in patients with partial obstruction of the bileduct which was accompanied by an appreciable increase in fæcal urobilinogen excretion.

In view of this conflicting evidence and the possibility that the fall in serum-bilirubin might be due to other mechanisms, such as an increased renal excretion of bile pigments or a decreased production of bilirubin due to slowing of the rate of red-cell or hæmoglobin breakdown, we decided to study the problem further. The observations described here suggest that the most likely explanation for the response in both hepatitis and obstructive jaundice is a change in the pathway of bilirubin excretion.

Material and Methods

24 jaundiced patients were studied before, during, and after steroid therapy. There were 13 cases of infective hepatitis, 3 of decompensated cirrhosis, and 8 of obstructive jaundice. These 8 comprised 5 cases of chronic intrahepatic obstruction due to various causes (table III) and 3 of classical extrahepatic obstruction due to carcinoma. The control period lasted three to four days. Prednisolone (40 mg. daily) was given for six days, except in some cases of infective hepatitis where it was considered unwise to stop after this period; in these prednisolone was continued until the serum-bilirubin had fallen to normal levels.

8 further patients with infective hepatitis who were treated in the same way, except that prednisolone was not given, served as controls. The treated and control groups appeared to be of comparable severity, judged by maximal serum-bilirubin levels, although the duration of preceding jaundice tended to be longer in the treated group. The cases, however, were not selected by the double blind technique.

Daily measurements included the serum-total-bilirubin by the method of Malloy and Evelyn (1937), the conjugated bilirubin being estimated by reading at fifteen minutes before the addition of methanol. Where the fall in serum-bilirubin appeared to be exponential the rate of fall was calculated using the expression $K = 0{\cdot}693/t^1/_2$, where K represents the slope of the straight line drawn through the points plotted on semi-logarithmic paper and $t^1/_2$ the time taken for the plasma concentration to decrease by half.

Urinary bilirubin excretion was measured daily in the majority of patients (Golden and Snavely 1948). In some of the later cases urine-urobilinogen was measured instead (Schwartz et al. 1944). Unfortunately it is not possible to measure both urine bilirubin and urobilinogen at the same time, as the latter must be preserved in an alkaline medium which destroys conjugated bilirubin. The stools were collected over appropriate three-day periods and homogenised by means of a Pascall ball mixer, fæcal urobilinogen being estimated by the method of Maclagan (1946).

Red-cell survival was determined by the radioactive chromium technique (Veall and Vetter 1958). The results were expressed as the $t^1/_2$, which is the time taken in days for the initial radioactivity to decrease by half, and were not corrected for chromium

elution. Preliminary experiments showed that the rate of elution was not affected by liver disease. Where there was much early loss the first values are excluded and the line of best fit is drawn through the subsequent readings. Blood-loss into the gut was checked by measuring the radioactivity of the stools in a ring type G-M counter.

Results

INFECTIVE HEPATITIS

In 7 of the 13 patients in this group there was a striking response to prednisolone therapy. The serum-bilirubin, which had been constant during the control period, fell sharply, and with this there was distinct clinical improvement. This initial response was followed by a second and longer phase during which the serum-bilirubin fell more slowly. These two phases are illustrated in fig. 1, where the serum-total-bilirubin in case 2 has been plotted on a logarithmic scale against time in days before and during steroid treatment.

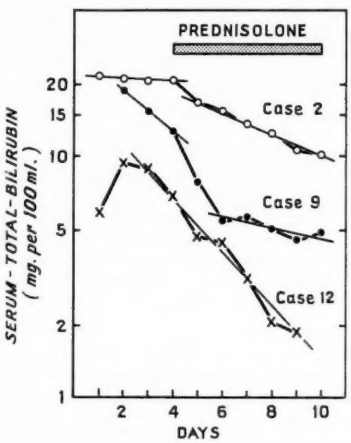

Fig. 1—Steroid therapy related to serum-bilirubin in 3 cases of infective hepatitis.
In cases 2 and 9 the response was characteristic. In case 12 the rate of fall of serum-bilirubin was unaffected by prednisolone, and was similar to that in patients recovering normally.

The patient was a girl of 21 years who had been jaundiced for eight weeks before admission. She had a high alkaline phosphatase (46 units) with negative flocculation tests. Throughout the control period the serum-bilirubin was over 20 mg. per 100 ml.; but within twenty-four hours after prednisolone was started it had dropped 4 mg. per 100 ml., which is equivalent to a 20% fall. This was followed by a slower fall which was exponential.

Exactly the same pattern of response was seen in the other patients who responded to steroid therapy, though in some the fall did not occur until the second day and the duration of the rapid initial phase varied from one to three days. In all cases the level of conjugated bilirubin fell parallel to the serum-total-bilirubin.

TABLE II—FÆCAL UROBILINOGEN EXCRETION DURING CONTROL AND SUBSEQUENT THREE-DAY PERIODS IN 4 PATIENTS WITH INFECTIVE HEPATITIS TREATED WITH PREDNISOLONE AND IN 2 OF THE UNTREATED GROUP

Case	Serum-total-bilirubin (mg. per 100 ml.)		Fæcal urobilinogen (mg. per 24 hr.)					
	Day 0	Day 9	Control	1st	2nd	3rd	4th	5th
1	12·2	3·0	113	126	105	127	..	..
2	20·6	7·3	20	20	18	33	63	198
5	12·9	4·8	24	62	137	82	132	115
10	11·2	4·6	35	69	176	123	167	..
A	12·7	6·0	72	51	75	158	59	59
B	13·0	1·7	87	154	182	98	139	..

One patient, case 8, showed no response to prednisolone. Her history was typical of infective hepatitis, though there was also radiological evidence of cholelithiasis. Prednisolone was continued for fourteen days, during which there was only a slight fall in serum-bilirubin. Readings were discontinued at this stage, which was unfortunate as shortly afterwards she began to improve with rapid clearing of the jaundice. In the remaining 5 cases the serum-bilirubin was already beginning to fall at the time prednisolone was started, and consequently any effect is more difficult to assess. In cases 9 and 10, however, there was a much more rapid drop in the first forty-eight hours of treatment and clinically there was pronounced improvement. After this period there was a very much slower rate of clearance, which also differed from that seen initially before steroid therapy was started. It seems likely, therefore, from the similarity of this response to that described previously that prednisolone affected the clearing of jaundice in these patients. In contrast, cases 11–13 showed no change in the rate at which jaundice cleared and there was a single exponential clearance from the time the serum-bilirubin started to fall (fig. 1).

As the decrease in serum-bilirubin during the various phases described appeared to be exponential, the percentage fall in serum-bilirubin per day can be calculated. These values are given in table I, from which case 8, in whom there was no change in serum-bilirubin, is excluded. There is a striking difference between the early and the later phases of the cases responding to prednisolone, the mean fall in serum-bilirubin being 32% per day for the short early period, compared with 7·4% per day for the later and longer phase. These figures differ from those obtained from the 8 controls with infective hepatitis who recovered without steroid therapy. In only 2 of these did it seem possible to divide the fall into two phases, and the difference between them was much less clear than in

TABLE I—RATE OF FALL OF SERUM-TOTAL-BILIRUBIN IN INFECTIVE HEPATITIS (CASES DIVIDED INTO TWO GROUPS ACCORDING TO THE TYPE OF RECOVERY OBSERVED)

Case	Initial recovery phase		Subsequent phase		Case	Single-phase recovery	
	Range (mg. per 100 ml.)	% fall (per day)	Range (mg. per 100 ml.)	% fall (per day)		Range (mg. per 100 ml.)	% fall (per day)
Controls:					*Prednisolone:*		
A	12·7– 9·3	13·9	9·3– 3·4	7·3	11	12·8–2·9	17·3
B	13·0– 8·5	27·7	8·5– 3·0	16·9	12	8·8–2·2	25·7
Prednisolone:					13	9·8–3·0	13·1
1	12·2– 6·4	63.0	6·4– 4·9	11·8	Mean		18·7
2	20·6–16·7	25·6	16·7–10·2	10·3	*Controls:*		
3	10·8– 4·7	40·7	4·7– 2·7	6·9	C	13·6–3·7	14·8
4	29·6–25·4	12·2	25·4–12·0	6·8	D	8·7–2·8	36·4
5	12·9– 8·2	23·1	8·2– 3·3	11·4	E	11·8–3·8	27·7
6	9·3– 6·9	15·4	6·9– 5·5	4·0	F	5·2–2·9	16·9
7	10·8– 6·5	25·7	6·5– 4·0	5·6	G	8·1–3·2	21·6
9*	12·8– 5·4	43·4 (18·7)	5·4– 4·8	4·2	H	14·9–3·1	14·2
10*	11·2– 7·7	19·2 (5·5)	7·7– 6·5	5·1	Mean		21·9
Mean (excl. A and B)		32·0		7·4			

* In these patients the serum-bilirubin was falling during the control period, the rate being shown in parentheses.

the treated group. The other 6 showed a single rate of clearance with a mean of 21·9% fall per day. The 3 cases in the treated group in which steroid therapy did not appear to alter the rate of fall had similar clearances to those of the controls.

Bile-pigment Excretion

In only four of the treated group (cases 1, 2, 5 and 10) were reliable measurements of fæcal urobilinogen obtained (table II). The results in the others were discarded owing to difficulties with constipation in the earlier stages when the patients were sick or because of suspected inaccuracies in collection. These 4, however, were among those showing a definite response to prednisolone. In 3 cases low levels of urobilinogen were found during the control period; the levels rose during the subsequent three-day periods, but the increase was relatively slight and was insufficient to account for the considerable drop in serum-bilirubin which had occurred; the highest level was never above the normal range. Case 1 had a higher level (113 mg. per twenty-four hours) during the control period at a time when his serum-bilirubin varied around 16 mg. per 100 ml.; subsequently there was only a slight rise despite a rapid fall in serum level. The results in 2 controls (A and B) who had similar initial serum-bilirubin levels, but in whom the duration of jaundice was shorter, are also shown in table II. The mean figure during the first period, when the serum-bilirubin was static, was higher than that observed in the treated group, although the general pattern of excretion was similar.

Urinary bilirubin excretion was estimated in 6 of those given prednisolone. It dropped sharply pari passu with the fall in serum-bilirubin and was often negligible even though some pigment remained in the serum. The excretion of urobilinogen in the urine, measured in 2 other cases, rose only very slightly at the time of the maximal fall in serum-bilirubin. The rise in urine-urobilinogen was greater in 4 of the untreated group and persisted longer.

Rate of Red-cell Breakdown

This was increased in all 9 patients in the treated group in whom it was measured. The mean red-cell half-life of the tagged cells was 16·1 days with a range of 14 to 17 days (the mean $t^1/_2$ in 6 normal subjects was 27·7 days, which agrees closely with previously published figures obtained by the same technique). None of the patients showed significant blood loss in the stools. There was no change in the rate of disappearance of the tracer radioactive cells during the period of prednisolone treatment. The red-cell survival was also reduced in 7 of the 8 patients with hepatitis not treated with prednisolone. The mean for these 7 was 17·9 days. There was no apparent reason for the normal result of 30 days in case H, the history and clinical course being comparable to that of others in the control group.

OBSTRUCTIVE JAUNDICE AND DECOMPENSATED CIRRHOSIS

The mean serum-bilirubin during the control period and the percentage fall over the subsequent period of treatment with prednisolone are shown in table III.

The first of the cases of *extrahepatic obstruction* did not respond to prednisolone. The next was seen soon after the onset of jaundice.

In this case prednisolone was used as a diagnostic test since the history was typical of infective hepatitis, with anorexia and malaise preceding jaundice. During the initial period the serum-bilirubin rose steadily. When prednisolone was given this rise halted, the level remaining virtually constant over the subsequent six days (fig. 2). During this time the urinary bilirubin excretion fell. After prednisolone was stopped serum and urinary bilirubin levels rose rapidly. The excretion of fæcal urobilinogen was low throughout, and at necropsy there was complete obstruction of the common bileduct by carcinoma.

TABLE III—RESPONSE TO STEROID THERAPY IN BILEDUCT OBSTRUCTION AND OTHER FORMS OF JAUNDICE

Case	Sex	Age (yr.)	Diagnosis	Serum-total-bilirubin*		
				Control	Prednisolone	% fall
Extrahepatic Obstruction:						
14	M	54	Carcinoma head of pancreas	36·1	36·9	..
15	F	73	"	12·3	16·1	..
16	F	62	Carcinoma hepatic duct	15·2	13·9	8·6
Intrahepatic Obstruction:						
17	F	48	Primary biliary cirrhosis	19·9	15·6	21·6
18	F	45	Portal cirrhosis	13·7	11·6	15·3
19	F	59	"	11·6	9·4	19·0
20	F	51	Unknown	17·4	15·6	10·4
21	M	33	"	36·7	35·4	3·5
Decompensated Cirrhosis:						
22	F	21	"Juvenile" cirrhosis	5·0	4·0	20·0
23	F	72	Portal cirrhosis	6·3	5·9	6·4
24	F	43	"	17·3	18·6	..

* These figures, in mg. per 100 ml., refer to mean values of control (4–6 days) and treatment (6–9 days) periods.

The remaining patient was thought to have portal cirrhosis on the basis of a misleading surgical biopsy specimen taken from the edge of the liver, but at necropsy was also found to have complete obstruction due to carcinoma. She was studied at a time when the serum-bilirubin was static. Administration of prednisolone was followed by a slight fall, the mean levels during the control and subsequent treatment periods being 15·2 and 13·9 mg. per 100 ml. As in the previous case the stools contained only a trace of fæcal urobilinogen throughout, and although in

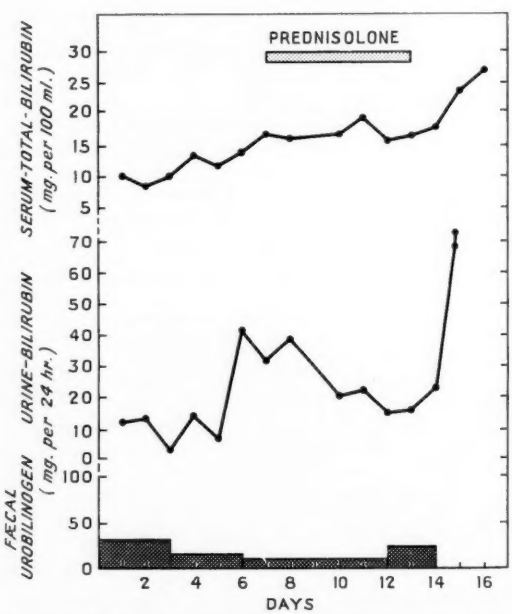

Fig. 2—Effect of steroid therapy in case 15, with complete bileduct obstruction.

both cases red-cell breakdown was increased (half-times of 17·3 and 17 days respectively) this was not apparently changed by the steroid therapy.

Of the 5 cases with *intrahepatic obstruction*, on the other hand, 4 showed a definite response to the administration of prednisolone, the serum-bilirubin falling 10–20% from the initial value. This fall was gradual over the first three days, and there was a prompt rise to the control level when treatment was discontinued (fig. 3). In none was there any appreciable change in fæcal or urine urobiliogen output (fig. 3). Urine-bilirubin excretion was followed in 1 case, in which it fell rather than rose. In all 5 patients there was evidence of increased hæmolysis with reduced half-times; but in only 1 (case 21) did the rate of red-cell breakdown appear to be decreased by prednisolone (Williams et al. 1961), and this was the patient whose serum-bilirubin level did not change significantly.

The response of the 3 cases with *decompensated cirrhosis* was disappointing. The fall in the patient with cirrhosis of

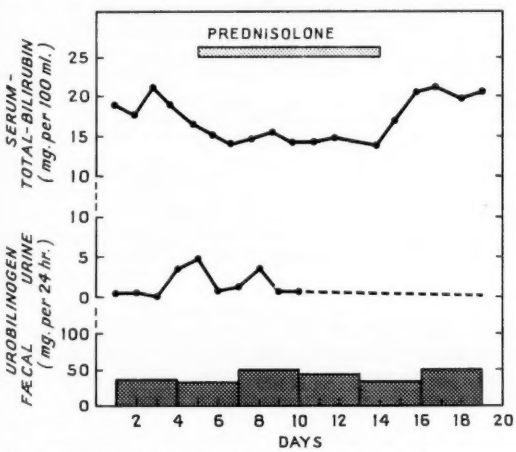

Fig. 3—Response of patient with primary biliary cirrhosis (case 17) to steroid therapy.

the active " juvenile " type (Bearn et al. 1956) is exaggerated when expressed as a percentage since the initial level was not very high. The other 2 patients with long-standing portal cirrhosis showed no real change.

Discussion

Clearly the immediate and rapid fall in serum-bilirubin in the patients with infective hepatitis responding to prednisolone cannot be accounted for by increased biliary excretion of bile-pigments, since fæcal urobilinogen excretion at this time was only slightly greater than in the control period. The lack of any significant increase in urinary urobilinogen supports this view. Later the fæcal urobilinogen excretion did rise; but even then the increase appeared to be relatively slight compared with the fall in serum-bilirubin, and in no case did it increase above the upper limit of the normal range. Nevertheless, with such a wide normal range (100–250 mg. per twenty-four hours) excretion of amounts within this range may be above the normal for the individual patient. The highest excretory levels occurred at various times after the beginning of steroid therapy, and case 1 had a surprisingly high excretion in the control period (113 mg. per twenty-four hours) which did not change significantly in the subsequent fifteen days though the serum-total-bilirubin fell from 12·2 to 3·0 mg. per 100 ml. Possibly the low levels observed during the early part of the response were due to the absorption of large amounts of urobilinogen from the gut into the enterohepatic circulation which were then re-excreted by the liver in some unknown form; but if this were so one would have expected a considerable increase in urinary urobilinogen, which did not occur in the 2 cases in which this was measured. In the patients with obstructive jaundice that responded to prednisolone the fall in serum-bilirubin was often appreciable (up to 20% of the initial level), but here again there was no evidence that it was due to increased biliary secretion since fæcal urobilinogen levels were low throughout. That the response in these patients was due to steroid therapy is shown by the very rapid return of the serum-bilirubin to its initial level when prednisolone was discontinued.

Another possible mechanism which can be excluded by the present study is that the serum-bilirubin falls as a result of increased renal excretion of the conjugated pig ment. In the patients with infective hepatitis there was a sharp decrease rather than an increase in urinary bilirubin, which probably reflected the decrease in serum level rather than any specific effect of the corticosteroid on renal clearance. A similar effect occurs in obstructive jaundice (Katz et al 1957). Although little is known about the concentration and distribution of bilirubin in the tissues, it seems unlikely that the fall in serum level could be due to a shift to the tissues or to some other change in distribution, as clinically the jaundice appeared to decrease and in none of the cases did the hæmatocrit or weight alter significantly.

There is also no evidence that the response is due to a decrease in the rate of red-cell breakdown. In only 1 patient did this rate decrease, and in this case the serum-bilirubin fell only very slightly. There remains the possibility that the rate of breakdown of hæmoglobin is reduced or that it is converted to colourless derivatives, which do not react with the diazo reagent; but this seems unlikely, particularly in hepatitis, since the magnitude of the fall is greater than that which would be theoretically expected if hæmoglobin breakdown was completely inhibited. Indeed in the majority of our patients the rate of red-cell breakdown was increased. Cawein et al. (1960) have reported similar findings in hepatitis and obstructive jaundice, and the relationship between this abnormal hæmolysis and the chronic low-grade hæmolytic state known to occur in cirrhosis (Chaplin and Mollison 1953, Jandl 1955) is of considerable interest. The possible mechanisms involved, together with the hæmatological changes found in the present cases are discussed elsewhere (Williams et al. 1961), but it is worth emphasising that such hæmolysis considerably increases the load of bilirubin to be excreted by the damaged liver. We were unable to find any correlation in infective hepatitis between the degree of hæmolysis and the maximal concentration of serum-bilirubin or the duration of illness.

The remaining, and most probable, explanation of the response in hepatitis is that the bile-pigments are excreted via another metabolic pathway. Indeed, the existence of an additional pathway of bilirubin breakdown has been postulated in normal subjects to account for the discrepancy, noted by many workers, between calculated bilirubin production and the observed lower levels of fæcal urobilinogen excretion, particularly since it has been shown (London et al. 1950) that 10–15% of fæcal urobilinogen is derived from a source other than the breakdown of red cells. Shen (1960) has shown that intravenous injection of hæmolysed blood leads to the theoretically expected increase in fæcal

urobilinogen, suggesting that in normal subjects there is a limit to the amount of bilirubin which can be excreted by non-urobilinogen pathways. Such a mechanism may also explain how in the Crigler-Najjar type of congenital hyperbilirubinæmia, where there is almost complete absence of glucuronyl transferase in the liver, the high serum-bilirubin level may nevertheless remain constant.

Even in our control patients with infective hepatitis the observed increases in fæcal and urine urobilinogen did not appear to be sufficient to account, at least in the early stages, for the fall in serum-bilirubin. It seems likely, therefore, that in patients recovering without steroid therapy the establishment of a normal flow of bile is not the only factor involved and that some of the bilirubin is excreted by another pathway. Yet there was a striking difference between the recovery phase in these patients with a single rate of pigment clearance (21·9% per day) and that in those responding to prednisolone. Here there were two distinct phases—namely, a rapid initial drop in serum-bilirubin (32% per day) followed by a very much slower fall of 7·4% per day. Such a response would be understandable if the effect of steroid therapy in hepatitis were not only to initiate recovery but also, for the first few days, to enhance the excretion of bilirubin via an additional metabolic pathway. Subsequently the serum-bilirubin level falls more slowly, and the fall is probably mainly due to increasing biliary flow. The rate of fall observed in our patients during this second, slow phase is similar to that found by Rundle et al. (1958) after successful surgical relief of obstructive jaundice. The existence of this slower phase of clearing explains the apparently anomalous finding of Ducci et al. (1957) that, despite the immediate and dramatic response to steroid therapy in infective hepatitis, the total duration of illness was not significantly different from that in a control group of cases of comparable severity.

The response of our patients with obstructive jaundice may also be due to a temporary increase in the excretion of bile-pigments through another metabolic pathway. Whether this is the same additional pathway as in infective hepatitis or even in normal subjects is undecided.

Finally, although this study was not designed to assess the value of prednisolone as a diagnostic test, the results do show that it may be of considerable help in distinguishing infective hepatitis with long-continued jaundice from extrahepatic obstruction. In the latter the fall in serum-bilirubin, in our experience, is rarely as great as in hepatitis. Moreover it occurs in the first few days of treatment, after which the level remains constant—which is quite different from the type of response in infective hepatitis. The main difficulty lies in the occasional case of hepatitis which fails to respond to steroid therapy.

Summary

The effect of steroid therapy on bilirubin metabolism was studied in infective hepatitis and other forms of jaundice.

In hepatitis responding to prednisolone, two distinct phases were noted: a rapid drop in serum-bilirubin in the first twenty-four to forty-eight hours, followed by a very much slower fall. In contrast, in patients recovering without steroid treatment there was a single rate of clearance.

In obstructive jaundice the fall in serum-bilirubin level was less marked, and when treatment was discontinued the value promptly returned to the initial level.

The response in obstructive jaundice and the initial fall in infective hepatitis could not be accounted for by increased biliary excretion, changes in renal clearance of bile-pigments, or decrease in the rate of red-cell breakdown. It was concluded that steroid therapy must cause or enhance the excretion of bilirubin via an additional metabolic pathway.

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POSSIBLE ABSENCE OF ESSENTIAL HYPERTENSION IN TWO COMPLETE PACIFIC ISLAND POPULATIONS

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THE relation of blood-pressure to age has been conclusively established in Europe and the United States. The means and variances of systolic and diastolic pressure increase with age. For systolic pressure, the rate of increase is greater after the age of 50 years, and this is associated with a greater spread and positive skewness of the frequency-distribution curves of blood-pressure. A similar pattern has been demonstrated in Assam (Wilson 1958), but other surveys have suggested that in some non-Western populations pressures may not rise substantially in later life. The conclusions of many of these surveys have been open to doubt, however, because of imperfect selection of subjects and standardisation of measurements (for reviews see Kean and Hamill 1954, Pickering 1955, Smirk 1957).

In some Pacific Islands, relatively isolated complete populations can be studied in which the question of bias in the selection of subjects does not arise. I report here the casual arterial pressure of two such complete Pacific Island populations—those of Gau in the Fiji Islands, and of Abaiang in the Gilbert Islands. The Fijians are a predominantly Melanesian race; the Gilbertese are Micronesians.

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TABLE I—ARTERIAL PRESSURE (mm. Hg) BY RACE, SEX, AND AGE

Race and age (yr.)	Males					Females				
	No.	Systolic		Diastolic		No.	Systolic		Diastolic	
		Mean	S.D.	Mean	S.D.		Mean	S.D.	Mean	S.D.
Fijian:										
20–29	100	123·0	11·2	81·0	9·4	167	119·8	11·6	81·2	9·7
30–39	104	123·3	11·9	82·8	9·5	112	124·4	14·7	84·1	9·7
40–49	73	123·4	12·4	83·4	7·8	59	129·7	18·7	85·4	9·7
50–59	42	128·1	17·2	83·3	11·9	35	136·4	22·2	86·1	10·1
60–69	17	134·4	20·1	79·4	10·1	14	142·5	21·7	83·6	7·7
70 plus	9	136·6	18·2	87·8	11·5	6	120·8	9·7	75·0	12·6
Gilbertese:										
20–29	120	128·3	16·5	78·6	10·1	171	116·4	13·6	73·4	8·8
30–39	117	125·9	14·5	79·2	10·3	123	118·2	17·5	73·9	11·0
40–49	68	126·8	15·0	80·4	9·4	83	122·8	19·5	78·4	11·9
50–59	89	123·2	15·9	77·9	9·4	67	125·7	16·0	76·0	10·8
60–69	41	132·8	18·3	81·7	11·9	27	124·1	19·0	75·9	10·0
70 plus	16	135·9	30·3*	79·1	11·3	10	126·0	20·0	77·0	12·3

S.D. = Standard deviation.
*This high standard deviation is accounted for by a single very high reading (230 mm. Hg).

The Populations

Gau

The mountainous island of Gau lies in the Koro Sea, near the centre of the Fiji group. Its population at the 1956 Census was 1546 males and 1536 females (McArthur 1958). The island was visited in January, 1958, with a team from the Central Medical School, Suva. The blood-pressures of 99% of the adult population were measured.

Abaiang

Abaiang is a coral atoll, and lies in the central Gilbert Islands. Its population was estimated at 2900 in 1959. Blood-pressures were measured in April, 1960. Fourteen of the sixteen villages of the atoll were visited, and all the adults of those village were measured. The two villages omitted were on small detached islets.

Measurement of Pressures

The methods for measuring casual blood-pressure and arm circumference have been described in detail elsewhere (Lovell et al. 1960). Subjects were seen in their own villages, rested and seated at tables or desks in one of the larger village houses. All measurements were made by the same observer.

Primary education has been in existence in both communities for at least fifty years, and birthdays are commonly celebrated. There is therefore a general awareness of age. Each subject was asked his age. All the Fijians answered promptly, and there was no reason to doubt their accuracy. Elderly Gilbertese were sometimes uncertain of their exact age.

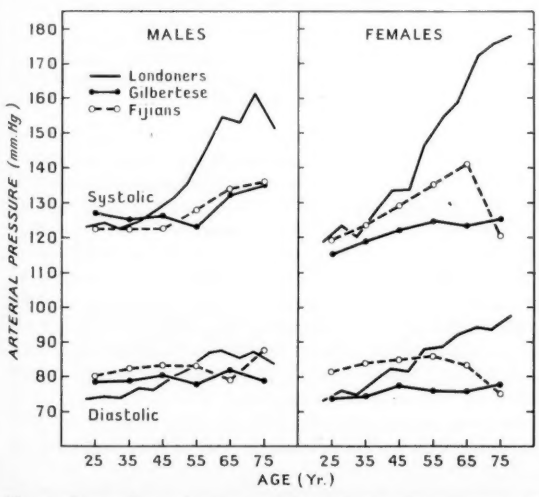

Fig. 1—Comparison of mean systolic and diastolic pressures of males and females related to age in a London population (Hamilton et al. 1954), Fijians, and Gilbertese.

Assistant medical officer Bwebwentekai Tekanene, a Gilbertese who acted as interpreter for the Abaiang survey, had spent his childhood on the island, and had also worked there for several years since graduation. When necessary, he estimated the age of subjects from his long acquaintance with them, from the age of their children, and from the impression of other Gilbertese.

Results

Mean Pressures

The results are summarised in table I. Fig. 1 illustrates them, and relates them to the Western type of curve (Hamilton et al. 1954). The mean systolic pressures of Fijians, Gilbertese, and Londoners are similar up to the fifth decade, but neither Pacific population shows the steeper rise of pressures in later years found in Londoners. Mean diastolic pressures change little with age in Fijians and Gilbertese, but rise in Londoners.

TABLE II—COMPARISON OF MEAN RISE OF PRESSURES WITH AGE AND LEVEL AT 45 YEARS

Race and sex	Mean rise of pressures with age (mm. Hg per yr.)		Mean pressures at 45 yr. (mm. Hg)	
	Systolic	Diastolic	Systolic	Diastolic
Fijian:				
Male	0·211	0·051	126·1	82·8
Female	0·454	0·114	129·4	84·2
Gilbertese:				
Male	0·058	0·035	127·4	79·3
Female	0·259	0·082	121·9	75·8
Londoners:				
Male	0·758	0·353	133·6	79·5
Female	1·143	0·464	139·4	82·7

The mean rise with age and mean level of pressures at age 45 years are shown in table II. In all three populations, mean systolic and diastolic pressures rise more with age in females than in males. For Fijians and Londoners, mean systolic and diastolic pressures of females at age 45 years are higher than those of males, but Gilbertese females have lower pressures than Gilbertese males.

Distribution of Pressures

The similarity of the blood-pressures of the three races in youth, and their differences in later years, are further illustrated in fig. 2, which compares the frequency-distribution curves of systolic blood-pressure in the age decades 20–29 and 50–59. Systolic pressures in the decade 20–29 are similar in all three populations. In the decade 50–59 the distribution curve of Gilbertese pressures, and to a lesser extent of Fijian pressures, retain the shape they showed at 20–29; but the curves for the pressures of Londoners are flattened and positively skewed, spreading out across higher levels of pressure.

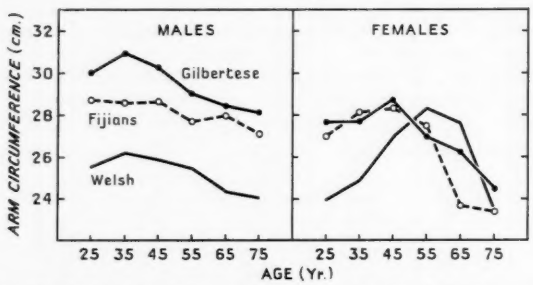

Fig. 2—Relation of mean arm circumference to age in both sexes of Fijians, Gilbertese, and a Welsh population (W. E. Miall, personal communication).

Arm Circumference

Mean arm circumference of Fijians and Gilbertese are shown in table III, where they are compared with the mean arm circumferences of a Welsh population (information kindly provided by Dr. W. E. Miall from his survey with Mr. P. D. Oldham [1955]). Except in Welsh females, arm circumference is similarly related to age and sex in all three races. Males and young females of both the Pacific populations have larger arms than the Welsh population.

Discussion

Neither the means nor variances of these blood-pressures of the two Pacific Island populations showed the substantial rises in later years which are characteristic of Western peoples. The population samples were complete island communities, and these differences cannot therefore be due to bias in the selection of subjects. There is no reason to suppose that the inhabitants of the two islands are not representative of their races. The pattern of their blood-pressures conforms to that found in earlier studies of less complete population samples of closely related Pacific peoples (Murrill 1949, Whyte 1958, Lovell et al. 1960).

The difference between the blood-pressures of these Pacific Islanders and Western peoples is not due to differences in arm circumference, because the relation between arm circumference and age is generally similar in both groups. There is no evidence that the rarity of high pressures among older Fijians and Gilbertese is due to an early selective mortality among those who might develop high pressures, nor that these peoples are subject to influences which depress their blood-pressures in later years. The most likely explanation of the difference is that essential hypertension does not occur, or is very rare, among Fijians and Gilbertese. This hypothesis would gain support if high blood-pressure among them could be shown to be secondary to other disease. A detailed investigation of all cases of hypertension in both peoples would be interesting.

The demonstration that populations exist in which the frequency-distributions of blood-pressure show very little change with age is interesting in view of the current controversy about the nature of essential hypertension (Pickering 1955, Platt 1959). It is consistent with the view that the high blood-pressure without evident cause which occurs in Western populations is qualitatively different from physiological blood-pressure, and constitutes a disease entity. In a Western population, those who are free from this disease may have a frequency-distribution curve of blood-pressure resembling that of Gilbertese. Those who suffer from it, however, may have a frequency-distribution curve of blood-pressure placed to the right of the other distribution, but overlapping it, so that addition of the two results in the spread, skewed curve which is characteristic of Western populations. Platt (1960) has performed such an addition using two hypothetical populations and obtained a curve similar to the one published by Hamilton et al. (1954) for London females aged 50–59 years. In fig. 3 I have replaced the larger of Platt's curves with the almost identical curve for Gilbertese females aged 50–59 years. One of the hypothetical populations drawn by Platt does in fact exist.

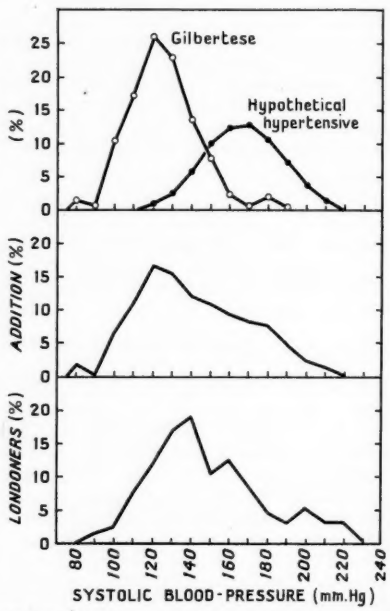

Fig. 3—Addition of small hypothetical "hypertensive" population to frequency-distribution curve of Gilbertese females aged 50-59 years, producing a spread, skewed distribution similar to that for London females aged 50-59 years (Hamilton et al. 1954).

On the other hand, the evidence from this study is also consistent with the opposing view that essential hypertension differs from physiological blood-pressure only in degree. It may be that Gilbertese and Fijians have not yet been subject to some environmental or genetic influences which raise the blood-pressure of a population in later life. The slightly greater spread and skewness of the frequency-distribution curves of blood-pressure for Fijians could indicate that Fijians are beginning to develop the Western pattern of blood-pressure, and the distribution of blood-pressures of Indians of Fiji (Lovell et al. 1960) might suggest that this trend has proceeded still further among them. The stresses of Western culture have not yet reached either Fiji or the Gilbert Islands in force; but traditional village life has been more distributed in Fiji, partly because of the very large immigrant Indian population.

Of the many environmental factors which might contribute to the differences in blood-pressure between these Pacific Islanders and Western people, climate seems

TABLE III—MEAN ARM CIRCUMFERENCE: COMPARISON BY AGE AND SEX FOR FIJIANS, GILBERTESE, AND A WELSH POPULATION (MIALL AND OLDHAM 1955)

Age (yr.)	Males			Females		
	Fijians	Gilbertese	Welsh	Fijians	Gilbertese	Welsh
20–29	28·70	29·89	25·50	27·08	27·66	24·02
30–39	28·62	30·91	26·11	28·14	27·71	24·84
40–49	28·62	30·18	25·83	28·39	28·78	27·00
50–59	27·74	28·98	25·47	27·50	27·00	28·34
60–69	27·96	28·42	24·33	23·67	26·29	27·66
70 plus	27·08	28·09	23·98	23·39	24·46	23·44

unimportant (Doyle and Lovell 1960). It has not proved possible so far to implicate diet, salt intake, smoking habits, or parity (personal observation). Other possibly relevant factors have yet to be examined. Prospective, long-term study of these and similar complete Pacific Island communities, as they become increasingly Westernised but remain geographically and genetically isolated, may provide important information on the nature of essential hypertension and its ætiology.

Summary

The existence of populations which do not show the substantially higher blood-pressures in later life that are characteristic of Western peoples has been established by surveys of all the inhabitants of two Pacific islands. Apparently essential hypertension does not exist among these people, or is rare.

These findings are consistent with the hypothesis that essential hypertension is qualitatively different from physiological blood-pressure, but are equally consistent with the view that essential hypertension differs from physiological blood-pressure only in degree.

Such complete, relatively isolated populations merit long-term prospective study to discover whether their blood-pressures change as they become " Westernised ".

I am indebted to Professor R. R. H. Lovell, who first suggested the importance of studying blood-pressure in the Pacific, for his valuable advice and helpful criticism. Dr. Dill Russell, director of medical services, Fiji, Dr. Roy Edmonds, principal of the Central Medical School, Suva, Dr. W. Rees, Chief Medical Officer of the Gilbert Islands, and A.M.O. Bwebwentekai Tehanene provided generous assistance which made the field work possible.

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DIAGNOSIS, PROGNOSIS, AND TREATMENT OF SEA-SNAKE BITE

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" Thy tayl is deth, thurgh thin envenymynge."—GEOFFREY CHAUCER. *The Merchant's Tale*, 1386.

SEA-SNAKES are an occupational hazard to Asian fishing folk: bathers are rarely bitten. Sea-snake venom is highly toxic, although yields are small. The general clinical features (Reid 1961) and pathology (Marsden and Reid 1961) of sea-snake-bite poisoning have been described elsewhere. This paper reviews diagnosis, prognosis, and treatment, and is mainly based on my observation of 38 patients admitted to hospital in 1957–59 after being bitten by a sea-snake; but some patients observed before this period and cases from the literature are also included.

The Patients

The sea-snake was reliably recognised in 25 of the 38 cases in 1957–59. In 4 victims typical toxæmia developed. Details of these 29 patients (all men) are shown in the table. The remaining 9 patients (only 1 was a woman) did not recognise a sea-snake, but were bitten in the sea, felt no local pain after the incident, and had bite marks corresponding to those of a sea-snake; no poisoning followed. These 9 are termed " probable cases ". 3 fishermen and all the 13 bitten when bathing (including 7 of the " probable cases "), trod on the sea-snake. 22 fishermen were bitten while handling nets. 10 fishermen and 11 bathers were bitten in Penang Island coastal waters, 15 fishermen in Malayan mainland waters, and 2 bathers in a mainland rivermouth. Since fishermen immediately throw sea-snakes back into the sea, they are rarely brought for identification; in fact, this happened only in 2 cases. In the remaining 23 identification was based on the fishermen's description of the snakes' colour and size. They all know the commoner species. In 15 cases (1 personally identified) the snake was *Enhydrina schistosa* Daudin. This is much the commonest species in Asian waters. In 6 cases *Hydrophis cyanocinctus* Daudin was responsible, and in 3 *H. spiralis* Shaw; these are both common species; in 1 case, I identified *Kerilia jerdoni* Gray.

Diagnosis

Fish-stings are much commoner than sea-snake bites, especially among bathers. Severe local pain follows; its presence excludes the possibility of a sea-snake bite, which, after the initial prick, is painless.

Serious envenoming followed only one third of the bites—only one quarter if the 9 probable cases are included (see table). This emphasises the importance of distinguishing snake-bite poisoning from poisonous-snake bite. Many doctors assume that if a snake is venomous, poisoning after a bite is inevitable. Envenoming after a sea-snake bite is shown by " remote " muscle aches, pains, and stiffness on movement coming on one half to one hour after the bite. Examination one to two hours after the bite reveals moderate or severe pain on passive movement of arm, thigh, neck, or trunk muscles. On neurological examination, findings, including power and tendon reflexes, will be normal at this stage. Myoglobinuria becomes evident on inspection three to six hours after the bite. Dusky yellowness with positive protein and occult-blood tests precedes by an hour or so the red-brown colour of spectroscopically positive myoglobinuria. Bite marks are rarely conspicuous, and are not much help in diagnosis. Local œdema occurs in some fish-stings and excludes a sea-snake bite (provided the œdema is not due to a tourniquet). A feeling of general coldness is *not* a reliable symptom of poisoning. Among fishermen it is a traditional complaint after sea-snake bite and is present whether or not toxæmia develops.

If a patient should come to a doctor within one hour of being bitten—i.e., before symptoms of poisoning start (an unlikely event)—judgment must be reserved. But if one hour has elapsed since the bite and there are no " remote " pains on muscle movement, serious poisoning can be excluded. The only exception to this " one-hour clearance " rule is when a victim applies an effective ligature within a minute or so of the bite and keeps it on until he reaches medical aid (see figure).

Prognosis

The 17% mortality (12% if the 9 probable cases are added) does not reflect the general death-rate in sea-snake bite since the cases are selected by coming to hospital. Many sea-snake victims do not come to hospital (Reid and Lim 1957).

The most rapid death recorded was two and a half hours after the bite (FitzSimmons 1912); the longest period between a bite and death was twelve days (Reid 1956c). This period has been noted in 48 victims previously reported or personally observed. 12 died within eight hours of the bite (early deaths are due to a combination of respiratory-muscle damage, inhalation of vomit, and retention of secretions), 23 between twelve and twenty-four hours (respiratory failure and hyperkalæmia are the main lethal factors), and 13 deaths occurred two or more days after the bite.

Multiple bite marks suggest a high venom dose, though single marks do not necessarily indicate a small dose. Vomiting, ptosis, weakness of external eye muscles, dilatation of pupils with a sluggish light reaction, and a leucocytosis exceeding 20,000 are all sinister signs. The remaining early clinical

features (Reid 1961) are equally common in patients who subsequently recover; but the tempo is quicker in those destined to die—a matter of hours rather than days. Signs of respiratory insufficiency with hypertension and cyanosis indicate the end is near. If an electrocardiograph is available, serial records are the most practical means of revealing hyperkalæmia for prognostic and therapeutic purposes. After the first three or four days after the bite, renal failure is the chief hazard, and may cause death with remarkably few warning symptoms. A "fixed" specific gravity of 1·010 to 1·013 is a danger signal; and if, in addition, the twenty-four-hour output falls below 500 ml. the outlook is grave.

Recovery may take weeks or months. The best guide is the duration of myoglobinuria—each day myoglobin is visible on inspecting the urine means approximately one week of illness. Permanent renal damage may result from sea-snake-bite poisoning, which is not surprising since tubular necrosis is common in those who die (Marsden and Reid 1961). Myonecrosis is the principal histological lesion in human victims of sea-snake venom; and in case 9 arm abduction was significantly weaker one and a half years after the bite, though no wasting was apparent.

Treatment

A lethal dose of sea-snake venom is absorbed from tails of dogs within three minutes of the bite (Reid 1956b); and clinical observations confirm this. By the time the patient reaches hospital (see table), any venom injected will be in the general circulation and much may be already acting on susceptible tissues. Application of a tourniquet, amputation, excision, and incision, with or without suction of the bite, can play no rational part in treatment at this stage (case 17 was a rare exception, see figure). Only 4 of the 38 victims seen in 1957–59 applied tourniquets after the bite; 2 victims incised it. This contrasts strongly with the treatment of land-snake bite; for which northern Malayan rural inhabitants customarily apply ligatures.

Case 17—The patient presented with an effective tourniquet (most exceptional) applied within one minute of being bitten by *E. schistosa* and not subsequently released. Amputation was offered and adamantly refused. No poisoning ensued.

Since land-snake antivenene is ineffective against sea-snake venom (Rogers 1905, Lamb 1906, Savoor 1955, Carey and Wright 1960), it was not given to any of the 38 patients. Steroids were given to all 9 subjects with serious envenoming, to 1 of the 2 trivial cases, and to 6 patients who were not poisoned. Cortisone 250 mg. by intramuscular injection was given as a loading dose in adults, and thereafter 200–400 mg. orally each day, the dose being tapered off after various periods up to fifteen days after the bite. Triamcinolone 20 mg. was given to case 2. It is impossible to know whether steroids helped any of the 10 who developed toxæmia; but as 5 died and 4 had severe poisoning, it seems unlikely that significant benefit resulted.

Since, in experiments, sea-snake venom blocks myoneural junctions (Kellaway et al. 1932, Wright 1956), neostigmine was given intravenously to 5 patients with

COURSE IN 29 PATIENTS BITTEN BY SEA-SNAKES

Patient				Snake	Course				Treatment				
Case	Age (yr.)	Bather (B) or fisherman (F)	Where bitten	Species of snake	Bite/general-muscle-movement-pain interval (min.)	Bite/hospital admission interval (hr.)	Bite/death interval (hr.)	Recovery time (days)	Steroids	Rapid infusion	Oral fluids	Injection of placebo	Other
1	32	B	Leg	*E. sch.*	35	½	13	..	+	+	..	..	I.P.P.R., noradrenaline
2	10	B	Foot		40	¾	14½	..	+	+	..	..	I.P.N.P.R.
3	50	F	Foot	*E. sch.*	60	36	52	..	+	..	..	..	Postural drainage, penicillin
4	41	F	Hand	*E. sch.*	35	12	18½	..	+	+	..	..	Tank respirator
5	17	F	Finger	*E. sch.*	60	6¾	14½	..	+	+	..	..	Insulin, 'Resonium-A.'
6	17	B	Leg	..	60	1¼	..	180	+	..	..	..	Neostigmine, tocopherol, thiamine, cyanocobalamin, penicillin
7	11	B	Foot	..	60	99	..	90	+	..	..	..	Tank respirator, neostigmine, thiamine, penicillin
8	21	B	Foot	..	60	24	..	30	+	..	..	..	Neostigmine
9	44	F	Leg	*E. sch.*	60	1	..	30	+	..	..	..	Penicillin
10	15	F	Foot	*H. sp.*	90	1½	..	2	..	..	+	+	
11	26	F	Hand	*E. sch.*	60	1½	..	2	+	+	..	..	
12	49	F	Thumb	*H. cy.*	..	10	..	..	+	+	..	..	
13	27	F	Finger	*E. sch.*	..	4	..	..	..	..	+	+	
14	40	F	Finger	*H. cy.*	..	4	..	..	..	..	+	+	
15	30	F	Foot	*H. cy.*	..	24	..	..	..	..	+	+	
16	29	F	Toe	*H. sp.*	..	2	..	..	..	..	+	+	
17	38	F	Toe	*E. sch.*	..	1½	..	..	+	+	..	..	Amputation refused
18	24	F	Finger	*H. sp.*	..	1	..	..	+	..	+	..	
19	55	F	Foot	*E. sch.*	..	6	..	..	+	..	+	..	
20	35	F	Finger	*E. sch.*	..	3½	..	..	..	..	+	+	
21	60	F	Finger	*E. sch.*	..	5½	..	..	..	..	+	+	
22	29	F	Finger	*E. sch.*	..	3½	..	..	..	..	+	+	
23	35	F	Finger	*H. cy.*	..	4½	..	..	+	+	..	..	
24	15	B	Foot	*E. sch.*	..	4½	..	..	+	..	+	..	
25	21	F	Forearm	*H. cy.*	..	1	..	..	..	..	+	+	
26	24	F	Finger	*K. jer.*	..	6	..	..	..	..	+	+	
27	52	F	Hand	*E. sch.*	..	4½	..	..	..	..	+	+	
28	19	F	Finger	*E. sch.*	..	4½	..	..	..	..	+	+	
29	40	F	Finger	*H. cy.*	..	5½	..	..	..	..	+	+	

E. sch. = *Enhydrina schistosa*. *H. cy.* = *Hydrophis cyanocinctus*. *H. sp.* = *Hydrophis spiralis*. *K. jer.* = *Kerilia jerdoni*.

severe poisoning (including cases 6, 7, and 8). No discernible improvement resulted. To promote renal excretion of venom and protect the kidneys, a rapid intravenous drip of one litre of 20% glucose was given to case 1. This was changed in some later cases to a mixture of 25% glucose, 10% calcium gluconate and molar sodium lactate, to counteract hyperkalæmia and renal damage (Meroney and Herndon 1954). Intravenous insulin and intragastric ion-exchange resin (Resonium-A) were also given in case 5 when the electrocardiogram (E.C.G.) indicated hyperkalæmia. These measures seemed to prevent or reverse hyperkalæmia.

Penicillin was given prophylactically to 2 cases, and to combat respiratory infection in 2 other patients; otherwise antibiotics were not administered, nor was antitetanus serum. Tocopherol, aneurine, and cyanocobalamin were given to 2 severe cases (6 and 7), since sea-snake poisoning resembles idiopathic myoglobinuria, for which vitamins have been advocated (Acheson and McAlpine 1953, Elek and Anderson 1953). No improvement was apparent.

Artificial respiration by tank respirator probably saved the patient's life in case 7; but he was asthmatic and respiratory failure might have been induced by a mild asthmatic attack (Reid 1960). Tracheostomy and intermittent positive-pressure artificial respiration (I.P.P.R.) for case 1, positive-negative respiration (I.P.N.P.R.), using the newer Radcliffe machine with a negative phase, for case 2, and a tank respirator for case 4, clearly lengthened survival time.

Discussion

The risk of death to bathers is greatly exaggerated, and is much less than that of accidental drowning. In 1955–59 only 2 bathers in Penang Island waters died from sea-snake bite, but 21 bathers from the same beaches died from accidental drowning.

In view of the high toxicity of sea-snake venoms, the low incidence of poisoning is remarkable. The species commonest in Malayan waters, *E. schistosa*, *H. cyanocinctus*, and *H. spiralis*, all have highly toxic venom and a yield capable of killing several adults. Serious toxæmia is also unusual in patients bitten by poisonous land-snakes in north-west Malaya. I have obtained large amounts of venom from these snakes shortly after they have bitten humans; and it seems that a defensive bite seldom injects much venom. I think this is the main reason for the low mortality and morbidity in snake-bite.

Active immunisation of fishermen has been suggested (Reid 1956a); but snake venoms are poor antigens—despite the many snake-handlers who regard themselves as immune. Animals require many inoculations before resistance develops, some individual animals never acquire immunity, and immunity when acquired lasts only a few months (Essex and Markowitz 1930, Kuwajima 1953, Carey and Wright 1960). To immunise fishing folk effectively against sea-snake-bite poisoning would involve an initial course of about six monthly injections and then booster doses two or three times a year for the rest of their fishing lives.

It has become increasingly obvious that local mechanical or first-aid measures are irrelevant to the *medical* treatment of sea-snake bite, because by the time the doctor sees the victim it is too late for them to do any good. It cannot be emphasised too often that most sea-snake-bite victims require no medical treatment other than reassurance. In my experience, this is best achieved by an injection of placebo (regardless of the patient's intelligence, social status, or creed).

Further treatment is needed: (1) if symptoms of envenoming are already evident; (2) if the patient is seen within one hour of being bitten, even though symptoms of poisoning are absent; (3) if the patient has an effective tourniquet in position.

It is not yet known whether appreciable venom is excreted by the kidneys in man; the results of injecting into animals urine from patients with severe sea-snake poisoning were equivocal. But it is rational to promote a diuresis, not only to encourage excretion of venom and secondary toxic products but also to minimise renal damage. The patient should drink a litre of water as quickly as possible or be given a rapid intravenous infusion of a litre of a mixture of 25% glucose, 10% calcium gluconate, and molar sodium lactate.

A chemical antidote (sea-snake antivenene) is produced by the Commonwealth Serum Laboratories, Melbourne, with *E. schistosa* venom from the Snake and Venom Research Institute, Penang. Carey and Wright (1960) showed that the resulting antiserum was also effective against the other two common venoms of *H. cyanocinctus* and *H. spiralis*. Recent research with specific antivenene in systemic viper-bite poisoning has demonstrated that antivenene administration is not as urgent as had been thought. Specific antivenene is highly effective in reversing systemic viper-bite poisoning even several days after the bite, so it is safe to wait until there is clear evidence of systemic poisoning before giving viper antivenene. It is hoped this will also apply to sea-snake antivenene, so that the only indication for its use will be clinically significant poisoning. In that case, not more than one in four victims will require antivenene. It should be given intravenously after a sensitivity test has been found negative: the safest way is by diluting it with saline (or with the glucose, calcium, and sodium lactate infusion) and giving it in a drip as a rule, serum reactions can then be controlled without difficulty.

Of the physiological antidotes, rest is the most important. In idiopathic myoglobinuria, Pearson et al. (1957) advocate almost complete immobilisation for three to four weeks to avoid tearing the fragile sarcolemmal sheaths which normally guide the regenerating muscle-fibres. In the early stages, postural treatment is vital to prevent inhalation of vomit; and it is particularly needed in the first week when, besides difficulty in turning, coughing may be feeble. The patient should be kept off his back so that gravity will assist tracheal drainage of chest secretions and infection and lung collapse are thus avoided.

At first sight, therapeutic hypothermia might appear to be a promising physiological antidote. The speed of all measurable reactions in muscle is diminished two or three times by a fall in temperature of 10°C (Hill 1956). Experimental cooling delays the fixation of tetanus toxin and retards the rate of injury to vulnerable tissues (Payling Wright 1955). Allen (1939) found that local hypothermia interrupted the development of signs of poisoning in animals injected with viper venom. In sea-snake envenoming, general hypothermia should slow the tempo of enzyme reactions in particular, and might enable the body to withstand a dose of venom which would otherwise be fatal. But Allen (1939) found that as soon as local refrigeration was stopped, gangrene became even more extensive than in untreated animals. Frogs survived longer at 3°C than at 18°C, but the cold did not alter the final toxicity of *E. schistosa* venom (Carey and Wright 1960). Similarly, in human victims of sea-snake envenoming it is likely that general hypothermia would only postpone the course. As soon as the temperature rose, the toxæmic processes would resume activity. Furthermore, hypothermia itself causes complex metabolic disturb-

ances. Large amounts of chlorpromazine and barbiturates, or a general anæsthetic, would be needed to prevent shivering. The harmful effect of these, in conjunction with the toxæmia, on the liver and vital centres might well cause death in a patient who could have survived the effects of venom alone. It is therefore unlikely that hypothermia will have a useful place in the treatment of sea-snake-bite poisoning.

Steroid therapy can be justified theoretically as a non-specific anti-toxæmic drug, as a muscle strengthener (Goodman and Gilman 1955), and as a means of increasing potassium excretion by the kidneys. In practice it was not notably successful.

The three main items in supportive treatment are combating (1) respiratory failure, (2) electrolyte disturbance (especially hyperkalæmia), and (3) renal failure. The results of I.P.P.R. and I.P.N.P.R. were disappointing. The general anæsthetic and the tracheostomy may have contributed to the fatal outcome. I prefer a tank respirator for respiratory failure. Tall, peaked T waves in the E.C.G. indicate the need for insulin; and if this does not succeed in shifting the potassium back into the cells, a potassium-removing ion-exchange resin should be given by gastric tube. If hyperkalæmia fails to respond to these measures, defeat is probable. Artificial kidneys will not be available for many years in hospitals treating these patients; and peritoneal dialysis is also impracticable. In the medical management of renal failure in the tropics, a basic water allowance per 24 hours of 700–1000 ml., rather than 500 ml., is indicated because of the greater sweat loss.

The doctrine of " masterly inactivity " has, with certain reservations, become increasingly appropriate—in keeping with the treatment traditional over the centuries among Chinese fishing folk, who forbid talking, smoking, eating, and movement for at least twenty-four hours after a sea-snake bite.

Summary

Although sea-snakes can be lethal, only a few of those bitten are seriously poisoned, because in defensive bites the dose of venom injected is usually small.

Correct diagnosis and prognosis are therefore very important, and they can confidently be made by simple clinical methods. Sea-snake antivenene will shortly be available, and may benefit some patients.

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THE SURGICAL TREATMENT OF PULMONARY EMBOLISM

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PULMONARY embolism not infrequently complicates a variety of medical, surgical, and obstetrical conditions, and it may cause death where otherwise the outcome might have been successful. Until comparatively recently Trendelenburg's operation of pulmonary embolectomy afforded the one hope, and elaborate preparations were often made for its emergency performance (Trendelenburg 1908, Meyer 1930, Hamilton Bailey 1943). But this was seldom successful, and so, with the introduction of anticoagulant therapy, attention readily turned towards methods of prevention. As a result there was a tendency to ignore the undoubted mechanical problem posed by the massive embolus.

Within recent years, however, renewed interest has been aroused in surgical treatment, not in opposition to anticoagulant therapy but as an adjunct, in certain cases (Lewis 1939, Steenburg et al. 1958, Arnulf 1960, Lewis 1960). The following case-history illustrates this aspect:

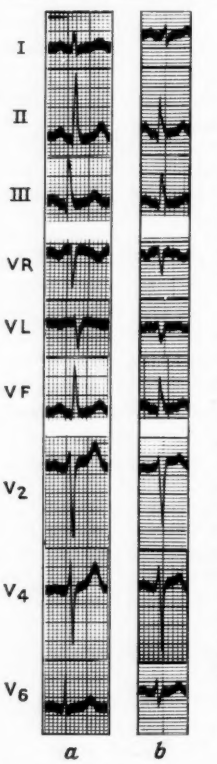

Fig. 1—E.C.G.s: (*a*) normal before operation, and (*b*) showing changes indicative of right ventricular dilatation.

Case-report

A 57-year-old man was admitted to the gastrointestinal unit of the Western General Hospital, Edinburgh, with a 4 months' history of constipation and weight loss. He was found to have diverticulitis of the pelvic colon, and an associated fistula-in-ano. Routine investigations, including electrocardiograms (fig. 1*a*) and chest X-ray, showed no other abnormality apart from hypochromic anæmia.

Because of continuing low-grade colonic obstruction, and uncertainty as to the possible presence of a carcinoma, the left colon was excised and a temporary proximal colostomy was formed. The postoperative course was complicated by chest infection and abdominal distension, culminating in a burst wound on the 8th day. After resuture of the wound the patient's general condition gradually improved. Then the fistula-in-ano became infected, and an ischiorectal abscess developed from this, requiring drainage on the 23rd day. The same night the patient had considerable perineal pain, controlled only by repeated injections of morphine.

The Embolism

At 8.30 next morning he suddenly became shocked and cyanosed, with feeble pulse and unrecordable blood-pressure. The jugular venous pressure was raised, and a triple

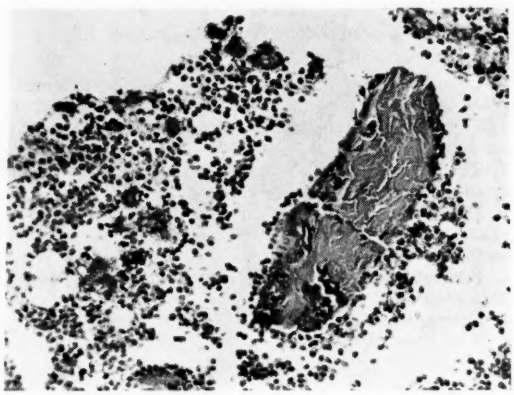

Fig. 2—Fragment of organised embolic thrombus removed from pulmonary trunk. (×225.)

rhythm was clearly heard over the lower end of the sternum. Pulmonary embolism was diagnosed clinically, and this was supported by an E.C.G. tracing which showed changes in limb-lead I and in V_6, suggesting the development of right ventricular dilatation (fig. 1*b*). In the absence of obvious venous thrombosis in the legs, the clot was thought to have originated in the pelvic and perineal veins as a sequel to the infection.

Oxygen and heparin given immediately produced no improvement. Continuous intravenous infusion of metaraminol ('Aramine') caused a transient rise of the systolic pressure to 130 mm. Hg, then it gradually fell despite increasingly rapid infusion. 45 minutes after the patient collapsed the blood-pressure was again unrecordable; he lost consciousness and appeared to be dying. Operative removal of the pulmonary embolus seemed to offer the only hope.

Pulmonary Embolectomy

Anæsthesia was induced with cyclopropane and oxygen, and these were continued intratracheally, respiration being controlled manually (A. C. M.). Intense bronchospasm was noted before induction, and as this gradually wore off the patient's condition improved. Later, when he became more responsive, tubocurarine 15 mg. was given intravenously.

The chest was opened through the second left intercostal space anteriorly, with division of the second and third cartilages to allow separation of the ribs. The pericardium was opened widely in front of the phrenic nerve to expose the heart, which was contracting feebly. The pulmonary trunk was not pulsating, but it felt firm and transmitted a curious slapping sensation synchronous with systole. While the trunk was being mobilised to allow the passage of a tape round it, the heart's action suddenly improved, the pulmonary trunk started to pulsate, and the slapping disappeared. It was decided to continue with the operation, and the trunk was steadied by traction on the tape and opened. There was free bleeding. No thrombus was seen or felt, and the trunk was shown to be patent to its bifurcation by passing along it a suction tube of wide bore. The incision in the trunk was then sutured, and the chest was closed, with drainage. Examination of the blood in the sucker trap showed numerous fragments of thrombus, each particle being about 3 mm. in diameter. These appeared to be part of a larger thrombus which presumably had either moved on or disintegrated when the trunk was handled. Histological examination confirmed that the fragments were composed of mature thrombus (fig. 2).

After operation the blood-pressure remained low for 24 hours, and metaraminol was again infused intravenously. Thereafter a normal circulation was maintained spontaneously, and consciousness gradually returned. The patient had no recollection of events from the time of his collapse.

Convalescence was uneventful, apart from moderate hæmoptysis and a short period of oliguria. Anticoagulant therapy was continued for 10 days after operation. Serial chest X-rays did not reveal any recognisable pulmonary infarction, and the E.C.G.s rapidly returned to normal.

Discussion

In this case death seemed to be inevitable unless the obstruction to pulmonary blood-flow was rapidly relieved. This view is arguable, and many believe that surgery in such circumstances is never justifiable. Barritt and Jordan (1960), discussing the value of anticoagulant therapy, suggest that Trendelenburg's operation no longer has any place in management. Nevertheless in some cases of pulmonary embolism death is protracted, sometimes for up to 8 hours, and conventional methods of treatment are unavailing (Maingot 1957). Recent years have seen gradually increasing support for surgery in selected cases (Steenburg et al. 1958, Arnulf 1960, Lewis 1960), the problem coming to be regarded as one of primary mechanical obstruction to the pulmonary circulation rather than secondary thrombosis.

Types of Pulmonary Embolism

Any clinical classification of pulmonary embolism must recognise the many degrees of severity of the condition. At one end of the scale there is sudden death from massive embolus, while at the other is the minor embolus which may be completely unrecognised, or which, by producing pulmonary infarction, may present with pleuritic pain and hæmoptysis.

Between the two extremes are cases in which surgical treatment is possible. Against operation is the fact that to date the success rate has not been high. (The first successful operation in the United States was in 1958 by Steenburg et al.) Some claim that the strain of the anæsthetic and operation might combine to do harm, killing a patient who would otherwise survive (White 1951); and there is the fear that wrong diagnosis might expose an ill patient to an unnecessary operation. On the other hand, medical treatment alone often fails even when there is time for the full regime to be brought into effect. Advances in anticoagulant and antibiotic therapy now offer advantages which were not available at the time of the earlier surgical endeavours.

Diagnosis

Sudden collapse with dyspnœa, cyanosis, and central chest pain in the postoperative patient should immediately suggest pulmonary embolism. The few alternative possibilities can usually be rapidly excluded. Progressive increase of jugular venous pressure developing from the time of collapse is a most valuable sign. Heart sounds are sometimes faint, but a third sound over the lower sternum is characteristic. X-ray of the chest may show right-sided cardiac enlargement, but pulmonary changes are few. Of more value is electrocardiography, when right ventricular strain is indicated by the development of an S wave in limb-lead I and a Q wave in lead III. T-wave inversion may also be seen in lead III and in the precordial leads over the right ventricle. Clinical assessment aided by E.C.G.s should permit reasonably confident diagnosis within 20 minutes.

Operative Treatment

The operation, as originally described by Trendelenburg (1908), was performed when the patient was at the point of death. Trendelenburg recommended awaiting this moment, the patient then being unconscious and pulseless, and no anæsthetic being necessary (Meyer 1930). Any circulation still present in the great vessels was interrupted by simultaneous occlusion of the aorta and pulmonary trunk before the trunk was incised. But to

await the point of death is physiologically unsound, and it is scarcely surprising that such a policy was seldom successful. Total interruption of the circulation for an appreciable time adds the risk of cerebral damage incompatible with survival. There is no doubt that Trendelenburg's advice still influences current thinking. That it originated amid uncertainties as to diagnosis and prognosis is forgotten, and advances in diagnosis and therapy since his time go unrecognised. Trendelenburg had to await the patient's impending death to counter the opposition to his original proposals.

The correct time to operate, in our view, is when the patient is failing to respond to conservative measures. Operation should then be performed as a planned procedure. The approach to the pulmonary trunk is rapid and easy, requiring no special skill or equipment. More and more surgeons are becoming conversant with thoracotomy for the purposes of cardiac massage, and positive-pressure anæsthesia is now commonplace. Because light anæsthesia with a plentiful supply of intratracheal oxygen should improve rather than harm the patient's general condition, the claim that stresses of anæsthetic and operation are unfavourable has probably little foundation in fact. The only feature of the operation which might be harmful is the manœuvre of strangling the heart, and this can be avoided by opening the left pulmonary artery instead of the main trunk (Lewis 1960), or by the introduction of clamps, such as the Pott's clamp. The technique of embolectomy differs in no way from similar operations elsewhere in the body; at the worst the clot can be broken and dislodged by massage, with immediate benefit, as in the present case.

Selection for Operation

Operation is only practicable when death is not immediate. It is important to realise that survival of the acute incident does not necessarily mean that recovery will be automatic, and a means of detecting those cases unlikely to survive without surgery would be of great value.

A review of cases of pulmonary embolism in the Western General Hospital over the past 5 years shows that, of sixty-five cases of pulmonary embolism confirmed post mortem, nine did not die immediately. Vigorous efforts at resuscitation had produced no response, and they had died within $^1/_2$–8 hours. The other fifty-six comprised those where death was immediate and those in whom the event was either unrecognised during life or was associated with terminal disease. On the basis of this study it seems that in a general hospital of 500 beds about two cases of pulmonary embolism might be suitable for surgical treatment each year. Although so few, these patients are often young, and the tragedy of the death of a young mother or breadwinner cannot be measured statistically.

To decide whether the apparently moribund patient might survive without operation, we analysed the records of fifty-one cases of non-fatal pulmonary embolism. In one only was there a clinical picture of impending death, with complete circulatory collapse; but this state was transitory, and within 30 minutes a normal blood-pressure had been restored after administration of oxygen, morphine, and heparin. Such an observation is, we believe, clinically important; and since the introduction of anticoagulants none of our medical or surgical colleagues can recall a case of pulmonary embolism which recovered from an apparently moribund state unless signs of recovery had appeared within 30 minutes.

On the basis of the present case, and our observations on other examples of pulmonary embolism, we suggest the following scheme of management:

1. Immediate resuscitative measures should be instituted—oxygen, morphine, heparin intravenously, and treatment for shock. At the same time the operating-theatre staff should be warned.
2. The blood-pressure should be recorded repeatedly, and the patient's condition assessed continuously.
3. Diagnosis should be confirmed by clinical examination of the heart and chest, and by demonstration of peripheral venous thrombosis.
4. Particular note should be taken of increase in jugular venous pressure.
5. Emergency E.C.G.s give valuable aid in diagnosis.
6. With these measures the diagnosis should be definite and the response to conservative measures assessed within 30 minutes.
7. If there is no response within 30 minutes then recovery without operation is unlikely; and, where there are no contra-indications, such as incurable disease, operation should be undertaken without further delay.

Summary

A moribund patient with major pulmonary embolism was submitted to operation, and he survived.

In selected cases of pulmonary embolism surgical treatment is indicated, and it should be possible to predict these with reasonable certainty.

A scheme of management is put forward.

Our thanks are due to Dr. W. I. Card and Dr. M. B. Matthews for their interest and encouragement, and for their helpful criticism in preparing this article. We are indebted to Dr. J. M. Drennan for help with the pathology and for translation of the German references.

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Preliminary Communications

CRICOID PRESSURE TO CONTROL REGURGITATION OF STOMACH CONTENTS DURING INDUCTION OF ANÆSTHESIA

WHEN the contents of stomach or œsophagus gain access to the air-passages during anæsthesia the consequences are disastrous. In spite of modern anæsthetic techniques—or sometimes, regrettably, because of them—regurgitation is still a considerable hazard during the induction of anæsthesia, particularly for operative obstetrics and emergency general surgery.[1–8]

By a simple manœuvre during induction of anæsthesia, regurgitation of gastric or œsophageal contents can be controlled until intubation with a cuffed endotracheal tube is completed. The same manœuvre may also be used to prevent inflation of the stomach (a potent cause of regurgitation) resulting from positive-pressure ventilation

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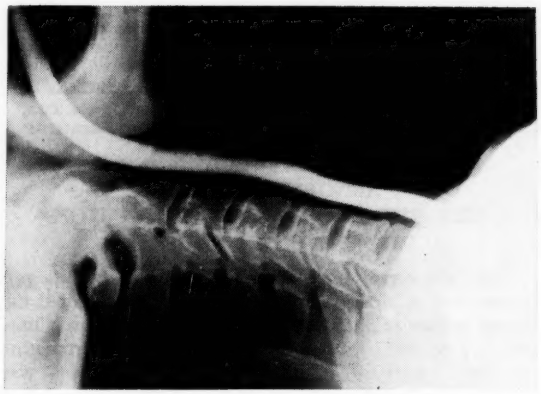

Fig. 1—Lateral X-ray of neck showing lumen of upper œsophagus filled by latex tube containing contrast medium.

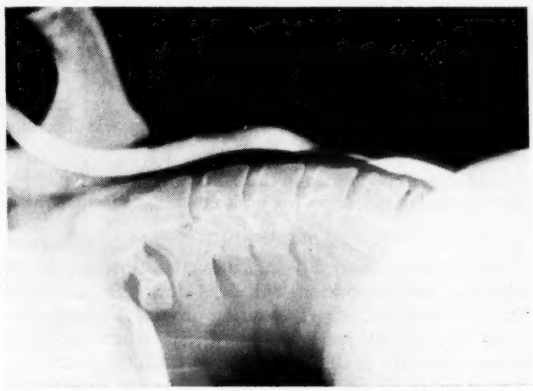

Fig. 2—Same as 1, showing obliteration of lumen by cricoid pressure at level of 5th cervical vertebra.

applied through a facepiece or by mouth-to-mouth respiration.

The manœuvre consists in temporary occlusion of the upper end of the œsophagus by backward pressure of the cricoid cartilage against the bodies of the cervical vertebræ. In the cadaver it was found that when the stomach was filled with water and firm pressure was applied to the cricoid, as described below, a steep Trendelenburg tilt did not cause regurgitation of fluid into the pharynx. Moreover, the flow of water from the pharynx could be controlled by varying the pressure on the cricoid cartilage.

Fig. 1 is a lateral X-ray showing a soft latex tube, distended with contrast medium to a pressure of 100 cm. H_2O, lying within the lumen of the pharynx and œsophagus of an anæsthetised and curarised patient. Extension of the neck and application of pressure on the cricoid cartilage (fig. 2) obliterates the œsophageal lumen at the level of the body of the 5th cervical vertebra.

USE OF THE METHOD

All reasonable steps should be taken to empty the stomach and œsophagus before anæsthesia is induced; but it is dangerous to assume that the stomach can be completely emptied by means of a Ryle's tube.[3]

Removal of Stomach-tube

After final aspiration, the Ryle's or œsophageal tube should be withdrawn. By "tripping" the sphincters at the upper and lower end of the œsophagus, a tube increases the risk of regurgitation, and it also interferes with the compression of the upper œsophagus. It can readily be replaced after intubation and the stomach can be drained before the end of the operation.

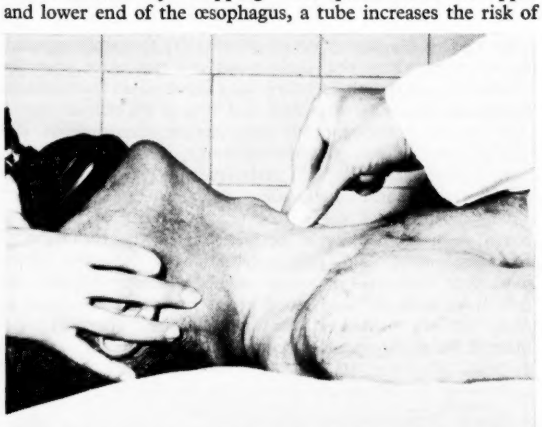

Fig. 3—Photograph showing extended position of neck and application of cricoid pressure.

Posture

During induction, the patient lies supine with a slight head-down tilt. The head and neck are fully extended (as in the position for tonsillectomy.) This increases the anterior convexity of the cervical spine, stretches the œsophagus, and prevents its lateral displacement when pressure is applied to the cricoid. Should active vomiting occur in this position, gravity will assist the flow of vomit away from the air-passages.

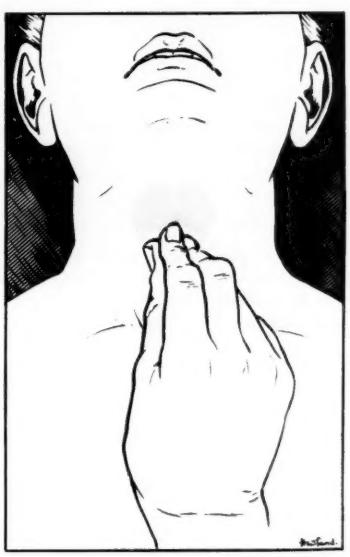

Fig. 4—Diagram showing manœuvre of cricoid pressure.

Choice of Anæsthetic

An intravenous-barbiturate/muscle-relaxant technique permits rapid intubation and is the method of choice. In the seriously ill, inhalational induction may be preferred; and, if a short-acting muscle relaxant is also used, conditions for intubation are obtained more quickly. Preoxygenation of the patient is a wise precaution whatever method is used. Before induction, it is essential to have easy access to a vein by means of an intravenous infusion, Gordh needle, or Sellick cannula.

Cricoid Pressure

Cricoid pressure must be exerted by an assistant. The nurse or midwife accompanying the patient can be shown in a few seconds how to do it. Before induction the cricoid is palpated and lightly held between the thumb and second finger; as anæsthesia begins, pressure is exerted on the cricoid cartilage mainly by the index finger (figs. 3 and 4). Even a conscious patient can tolerate moderate pressure without discomfort; but, as soon as consciousness is lost, firm pressure

can be applied without obstruction of the patient's airway. Pressure is maintained until intubation and inflation of the cuff of the endotracheal tube is completed.

Inflation of the Lungs

During cricoid pressure the lungs may be ventilated by intermittent positive-pressure without risk of gastric distension.

Intubation

Intubation is performed in the usual way. Indeed, posterior displacement of the larynx from cricoid pressure facilitates it.

DISCUSSION

The "old-fashioned" inhalational induction, in the supine or lateral position with head-down tilt, has something to commend it. If vomiting occurs, it usually does so at the lighter levels of anæsthesia when protective reflexes are still present. But any difficulty or straining during induction predisposes to regurgitation [9] and serious anoxic episodes may follow. In this position the use of muscle relaxants has heretofore been contraindicated because of the risk of gastric reflux following œsophageal relaxation.

The recommendation of Morton and Wylie in 1951 [3] and a *Lancet* annotation in 1956 [6] has led to the widespread use of the barbiturate/muscle-relaxant/rapid-intubation technique in the sitting position, for the management of potential regurgitation. This has two disadvantages:

1. Rapid induction of anæsthesia in the sitting position predisposes to cardiovascular collapse in the patient who is seriously ill.

2. The sitting position is no protection if active vomiting takes place in the brief interval between loss of consciousness and onset of muscular relaxation.[9] In fact, the entry of stomach contents into the lung is facilitated.

Experience of this second complication in two cases—both fortunately retrieved by immediate bronchoscopy—has been an additional stimulus to find an alternative.

Cricoid pressure offers a third way of managing patients liable to regurgitate stomach contents. It should not be used, however, to control active vomiting, because the œsophagus might be damaged by vomit under high pressure.

RESULTS

Anæsthesia in 26 high-risk cases has been induced by this method. In 23 of them (forceps delivery 1, œsophagoscopy for achalasia of the cardia 2, gastrectomy for adult pyloric stenosis 3, and laparotomy for intestinal obstruction 17) no regurgitation or vomiting took place before, during, or after cricoid pressure. In the remaining 3 cases (1 forceps delivery, 1 resection for carcinoma of the lower end of œsophagus, and 1 laparotomy for relief of obstruction of the small intestine) release of cricoid pressure after intubation was followed immediately by reflux into the pharynx of gastric or œsophageal contents, suggesting that in these 3 cases cricoid pressure had been effective.

SUMMARY

Backward pressure of the cricoid cartilage against the cervical vertebræ can be used to occlude the œsophagus (*a*) to control regurgitation of stomach or œsophageal contents during induction of anæsthesia, or (*b*) to prevent gastric distension from positive-pressure ventilation applied by facepiece or mouth-to-mouth respiration. It is contraindicated during active vomiting.

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I am grateful to Dr. C. G. Whiteside for advice in demonstrating œsophageal occlusion radiologically, to Miss Hewlands for the diagram, and to the photographic department of the Middlesex Hospital for the photographs.

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ABNORMALITIES OF SEX CHROMOSOME CONSTITUTION IN NEWBORN BABIES

THE first survey of the frequency of abnormalities of nuclear sex at birth was that of Moore,[1] who studied the buccal smears of 3715 newborn infants in 1959 in Winnipeg. 5 of 1911 males were found to be chromatin-positive (2·62/1000), but none of 1804 females was chromatin-negative. More recently Bergeman [2] has reported data from a similar survey of consecutive live births in Berne: 4 of 1890 males were chromatin-positive (2·12/1000), while 1 chromatin-negative child was noted among 1838 females. In this paper we report preliminary results from a similar survey at present in progress in Edinburgh, in which chromosome studies have been done wherever possible on the babies with abnormal nuclear sex.

STUDY POPULATION

The babies examined were those born in the maternity units of the Western General Hospital, Edinburgh, the Elsie Inglis Memorial Maternity Hospital, the Eastern General Hospital, Edinburgh, and Bangour Hospital, and in ward 51 of the Simpson Memorial Maternity Pavilion. Although every effort was made to ensure that the survey recorded all the consecutive live births, 19 babies were not examined: 2 who died shortly after delivery and 7 delivered by cæsarean section were missed in the early stages of the survey, and the others were lost to the survey because their mothers left hospital early, and failed to return for postnatal examination. This report refers to a study of 3000 male and 3000 female babies, who are entered as liveborn on the labour-room records. It is important to remember that, while this is the population most easily surveyed, it is not necessarily representative of the general population at birth.

TECHNIQUES

Nuclear sex was determined by the buccal-smear technique of Moore and Barr,[3] using a slight modification of their staining procedure.[4] In each case a hundred suitable nuclei were examined. If the smears were unsatisfactory they were repeated. In all cases where the nuclear sex did not agree with the phenotypic sex the observations were repeated on fresh smears. In this laboratory between 36% and 76% of the cells of females who are not known to have chromosome abnormalities, and also of cases of Klinefelter's syndrome, have been found to have a single sex-chromatin body (mean 49%). Such bodies are never found in normal males.

Chromosomes of the leucocyte component of peripheral blood were studied by a modification of the technique of Moorhead et al.[5] and skin preparations were made by the method of Harnden.[6] It would have been desirable to examine cells from both skin and blood in each case, and especially in those that are mosaics. This was not possible, however, and most of the observations are based on skin cultures alone.

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TABLE I—FINDINGS IN BABIES WITH ABNORMALITIES OF NUCLEAR SEX

Case no.	Phenotypic sex	Sex-chromatin analysis*			Chromosome studies							Sex-chromosome complement
		0	1	2	Tissue	Count distribution						
						<44	44	45	46	47	>47	
1	M	54	46	..	Blood	..	..	..	2	33	..	XXY
2	M	63	37	..	Skin	..	1	..	..	24	..	XXY
3	M	57	43	..	Skin	..	..	..	..	30	..	XXY
4	M	62	38	..	Skin	..	..	2	27	27	..	XY/XXY
5	M	90	10	..	Blood	..	..	..	26	3	..	XY/XXY
					Skin	..	1	2	19	8	..	
6	M	94	6	..	Skin	..	..	..	57	3	..	XY/XXY
7	M	79	21	..	Skin	..	..	2	15	1	..	XY/?XXY
8	M	59	41	..	Not examined							..
9	M	56	44	..	Not examined							..
10	F	100	..	..	Blood	..	3	26	1	..	..	XO
					Skin	..	..	20	..	..	..	
11	F	21	43	36	Skin	..	..	..	3	46	..	XXX
12	F	34	38	28	Skin	..	..	..	..	32	..	XXX
13	F	28	48	24	Skin	..	..	..	3	27	..	XXX
14	F	21	54	25	Not examined							..

*Expressed as % of cells with 0, 1, and 2 sex-chromatin bodies.

RESULTS

Abnormalities of nuclear sex were present in 9 males (a frequency of 3·00/1000), and in 5 females (1·67/1000). The results of sex-chromatin analysis and of chromosome studies in these cases are shown in table I, and the relevant clinical and family data are shown in table II. In 3 cases chromosome studies were not made for the following reasons: in case 8 permission for further investigation was refused, case 9 died before tissue for culture could be obtained, and in case 14 the cultures were unsuccessful.

Abnormalities in Males

In cases 1, 2, and 3 the results of sex-chromatin counts and chromosome analysis indicated that the sex-chromosome complement was XXY. Cases 4 and 5 are clearly defined examples of chromosome mosaicism of the XY/XXY type. In case 4 the proportion of cells in the buccal smear with a sex-chromatin body was within the expected range, while in case 5 it was found on three separate occasions to be much lower than is usual in cases of Klinefelter's syndrome.

Sex-chromatin counts within the normal range do not, therefore, necessarily exclude the possibility of the subject being a mosaic, but low counts on repeated smears of good quality from phenotypic males are suggestive of mosaicism. In case 6, for example, only 6% of the cells had a sex-chromatin body. Out of sixty cells examined from a skin culture, three had a count of 47 chromosomes, and in each the findings were compatible with an XXY sex-chromosome constitution. This evidence, taken together with the abnormally low frequency of sex chromatin, seems to justify the conclusion that this child is an XY/XXY mosaic. Permission for further examination to confirm this result was refused. This baby was the firstborn of male twins, the second twin being normal in respect of both sex chromatin and chromosomes.

In case 7, the proportion of cells with sex-chromatin bodies was low on several occasions, the best smear giving an average of 21%. Fifteen out of the eighteen cells examined from a skin-culture preparation had normal male chromosomes; only one had 47 chromosomes, but this was compatible with an XXY sex-chromosome constitution. This result is not conclusive; but, while further studies are obviously desirable, permission for further investigation has not been given. It seems probable, however, that this child also is an XY/XXY mosaic.

In cases 8 and 9 chromosome studies were not done, but both had sex-chromatin counts within the range expected in cases of Klinefelter's syndrome. Tissues obtained at necropsy from case 9 were also chromatin-positive.

Abnormalities in Females

The 1 chromatin-negative child (case 10) out of the 3000 females was found on examination of skin and blood cultures to have 45 chromosomes and an XO sex-chromosome constitution. In contrast the other 4 abnormal females had two sex-chromatin bodies in a proportion of the cells of the buccal mucosa. 3 of these (cases 11, 12, and 13) were shown to have 47 chromosomes and an XXX sex-chromosome constitution. In both cases 11 and 13, three cells were found with 46 chromosomes. In case 13 one, and in case 11 two, of these cells were consistent with an XX constitution; this is not considered to be significant. In the 4th case, both blood and skin cultures failed, but the sex-chromatin findings are consistent with an XXX sex-chromosome constitution.

DISCUSSION

Frequency

The data here reported on the frequency of chromatin-positive male babies are compatible with those of Moore [1] and Bergeman.[2] Combining the data of all three surveys,

TABLE II—CLINICAL AND FAMILY DATA

Case no.	Propositus		Parents' years of birth		Sex and year of birth of liveborn sibs					Comment
	Sex	Date of birth	Father	Mother	1	2	3	4	5	
1	M	June 20, 1960	1931	1935	F 1956	..	..	..	..	Appeared normal at birth
2	M	Nov. 18, 1960	1928	1933	F 1956	..	..	..	..	,,
3	M	Feb. 2, 1961	1934	1934	M 1959	..	..	..	..	,,
4	M	Jan. 17, 1961	1921	1926	F 1950	F 1956	..	..	..	,,
5	M	Feb. 1, 1961	1936	1940	..	..	..	..	..	,,
6	M	Jan. 1, 1961	1927	1928	F 1949	M 1961	..	..	..	Appeared normal at birth; 2nd sib was twin of propositus
7	M	Nov. 27, 1959	1925	1923	M 1950	M 1952	M 1953	M 1955	F 1957	Appeared normal at birth; 4th sib was a mongol
8	M	Jan. 26, 1961	1939	1943	..	..	..	..	..	Appeared normal at birth
9	M	Jan. 22, 1961	1939	1940	..	..	..	..	..	Died (pulmonary hyaline membrane disease)
10	F	Dec. 14, 1960	1932	1936	..	..	..	..	..	Neck webbing and lymphœdema
11	F	May 9, 1960	1923	1925	M 1948	..	..	..	..	Appeared normal at birth
12	F	March 12, 1961	1941	1942	..	..	..	..	..	,,
13	F	March 20, 1961	1935	1936	M 1956	F 1957	F 1959	..	..	,,
14	F	Oct. 8, 1960	?	1937	F 1955	..	..	..	..	,,

the frequency at birth of these children seems to be 2·65/1000.

1 female baby was found to have an XO sex-chromosome constitution. The numbers in all three surveys are too small to give an accurate estimate of the frequency of XO females, but all agree that this is relatively low. Combining the figures of the three surveys, and assuming that the chromatin-negative case reported by Bergeman was XO, the frequency is 0·30/1000 births.

Our data, as far as they go, suggest that the frequency of XXX females at birth is about 1·33/1000 births. In the other two surveys none was observed. At the time Moore's observations were made the significance of two sex-chromatin bodies was not appreciated, and the absence of triple-X females from Bergeman's results may well be due to chance.

Variations in the Sex-chromatin Pattern

In 3 of the 4 mosaics the proportion of sex-chromatin bodies in the buccal-smear cells was low. We would emphasise again that we believe that low, even very low, sex-chromatin counts in phenotypic males are significant. This is probably also true for phenotypic females.[7] Variations in the size of the sex-chromatin body, although not detected in this series, are also thought to be significant.[7]

Development of the Abnormal Babies

All the babies with XXX or XXY cell-lines were normal healthy infants with one exception (case 9), and this child died shortly after birth from pulmonary hyaline-membrane disease. The XO female was noted to have peripheral lymphœdema and neck-webbing at birth. This is in keeping with other observations that an XO karyotype is usually associated with one or more of a range of congenital abnormalities. In some cases, it is possible that these may be incompatible with survival for full gestation. If this is so it may explain the relatively low frequency of these cases, which should in theory be conceived more often than either XXX or XXY cases. During the period of the survey the buccal smears of 101 stillborn infants (49 males and 52 females) were examined. It was not possible to examine all the stillborn infants, but there is no reason to think that the sample is biased. Of the 49 males examined, two had chromatin-positive buccal smears. In one, this was confirmed on postmortem tissue samples; but in the other the postmortem tissues were macerated, and it was not possible to decide whether they were chromatin positive or negative. Thus of 11 chromatin-positive male babies 2 were stillborn, and 1 died shortly after birth. This suggests that further studies to determine whether infants with sex-chromosome abnormalities run an increased perinatal-mortality risk would be profitable.

The way these babies with chromosome abnormalities will develop in the future can only be a matter for speculation, because absence of information on a normal adult population makes accurate prediction difficult. It seems likely, however, that the XXY babies will develop into cases of Klinefelter's syndrome, with seminiferous-tubule dysgenesis, and possibly also mental retardation. The XY/XXY mosaics present an interesting problem. The resultant phenotype may well depend on the distribution of the two cell-lines in the primitive gonads: if cells with XY sex-chromosomes predominate in the testes, there may be little if anything to distinguish these cases from normal males.

The future of the triple-X females is even less predictable; but, on present evidence, it seems probable that in the majority sexual development will be normal, though mental development may be impaired. It seems likely that the XO female will be mentally normal, but that she will be sexually infantile and will never menstruate. We hope it will be possible to study the progress of these cases at regular intervals, at least until puberty, to determine how in fact they do progress.

Mosaicism

Several chromosome mosaics in man have previously been reported.[7 8] It was nevertheless surprising to find that 3, and probably 4, of the 9 chromatin-positive males were mosaics. One should also remember that it would be possible for a sex-chromosome mosaic to have a normal buccal smear; the finding of 4 mosaics among 6000, therefore, gives the lowest possible value of mosaicism in this population.

Bias in the Population

We have already pointed out that the group surveyed is not necessarily representative of the general population, nor even of the population at birth. In this country examination of babies born in hospital will be biased in favour of firstborn children and the children of difficult confinements. If, as suggested by Penrose,[9] there is a tendency for children with sex-chromosome abnormalities to be conceived by older rather than by younger parents, then the frequency of such abnormalities in this survey may well be different from what would have been found had it been possible to examine a representative sample of all children born; as already mentioned, any mosaics with a normal buccal smear would not be detected. It is reasonable, therefore, to suggest that the prevalence of sex-chromosome abnormalities in the general population at birth may be higher than among this hospital population of newborn infants.

The survey was made with the help of J. M. Mitchell, A.I.M.L.T., and Elizabeth R. Greenhill, A.I.M.L.T. One of us (N. M.) was given a grant from the Medical Research Council for technical assistance and apparatus.

We are particularly indebted to Dr. J. W. Farquhar, Dr. J. O. Forfar, Dr. A. Keay, Dr. D. T. D. Nicholson, and Dr. J. W. Worling for their help in initiating this survey; and to Dr. A. J. M. Drennan for his interest and for providing laboratory facilities.

For allowing us to carry out the survey we are grateful to Dr. A. F. Anderson, Dr. W. D. A. Callam, Prof. R. W. B. Ellis, Dr. D. J. M. Irvine, Prof. R. J. Kellar, Dr. C. D. Kennedy, Dr. W. A. Liston, Dr. E. Little, Dr. J. D. O. Loudon, Dr. J. E. W. Mackie, Dr. T. N. MacGregor, Dr. G. D. Matthew, Dr. P. R. Myerscough, Dr. S. J. Patterson, Dr. M. G. Pearson, and Dr. J. Sturrock.

We should also like to thank the staff of the M.R.C. Clinical Effects of Radiation Research Unit, all of whom have played some part in this survey; Miss M. Brunton, Miss S. Brunton, Miss M. Lawson, Mr. A. Ross, and Miss G. Woodcock for their technical assistance; and the nursing-staff at the maternity units, without whose help our study would not have been possible.

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Reviews of Books

The Treatment of Hypertension

Sir GEORGE PICKERING, M.D., F.R.C.P., F.R.S., regius professor of medicine, WILLIAM CRANSTON, M.D., M.R.C.P., first assistant, MICHAEL PEARS, M.D., M.R.C.P., clinical tutor, department of regius professor of medicine, University of Oxford. Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1961. Pp. 175. 56*s*.

THIS volume in the series of American Lectures on Living Chemistry is outstanding for its chapters on the chemistry and pharmacology of drugs in common use for lowering the blood-pressure. The material, though not new, is clearly presented and conveniently assembled; and there is also a sensible chapter on general management. It might be argued that it would have been better to produce a relatively inexpensive book on these aspects alone, especially since they will inevitably change quite soon. Alternatively, there is perhaps room for a comprehensive British review on the management of hypertension, though an excellent one by Edwards [1] has recently come from America. The practising physician will need to know a good deal more than he can find here about the assessment of the patient and the indications for lowering the pressure.

The first chapter, on the nature of essential hypertension, is a restatement of the senior author's views on essential hypertension as a quantitative deviation from the norm and not a qualitative disorder. Double-blind placebo-controlled trials are advocated for the assessment of newer drugs, but many physicians think that this procedure, however necessary for milder drugs, is of uncertain value; and in the matter of subjective effects it may not be justifiable or even scientific in patients with severe hypertensive disease. Not only is there danger in intermittent lowering of a high pressure but also the underlying condition in severe cases is so soon modified that consecutive periods of observation are not necessarily comparable. Space might have been saved by omitting descriptions of drugs now little used, such as thiocyanates and 'Veriloid', and the sections on sympathectomy and adrenalectomy.

Encyclopædia of Urology

Editors: C. E. ALKEN, Homburg/Saar; V. W. DIX, London; H. M. WEYRAUCH, San Francisco; E. WILDBOLZ, Berne. Berlin: Springer. 1961.

Vol. XIII/1. *Operative Urology*. WALTER BISCHOF, DR. MED., Neurochirurgische Universitätsklinik, Köln-Lindenthal; PETER BISCHOFF, DR. MED., Dozent für Urologie der Universität, Hamburg; CURT FRANKSSON, M.D., professor of surgery, Karolinska Institutet Medical School, Stockholm; RUDOLF FREY, F.F.A. R.C.S., Professor für Anæsthesiologie an der Johannes Gutenberg-Universität, Mainz; J. HARTWELL HARRISON, M.D., clinical professor of genitourinary surgery, Harvard Medical School, Boston, Mass; JOHN HELLSTROM, M.D., professor of surgery, Karolinska Institutet Medical School, Stockholm; WILHELM TÖNNIS, Professor DR. MED., Neurochirurgische Universitätsklinik Köln-Lindenthal. Pp. 460. DM 176.

VOLUME XIII/1 is the first of two volumes devoted to surgical technique. After an introductory section on anæsthesia the rest of the book deals mainly with operations on the kidneys and adrenal glands and ends with a detailed account of the surgical treatment of neurogenic disorders of the entire urogenital tract. The section on anæsthesia (Frey) is in German and includes reference to local and spinal techniques as well as conventional methods supplemented by hypothermia, hypotension, and muscle relaxants. Useful information is given on the selection of suitable anæsthetics for specific operations and on premedication, transfusion, and postoperative management.

The surgical approach to the kidney is dealt with (in English) by Hellstrom and Franksson, who go on to describe a wide variety of operations for renal disease including sections on renal vascular surgery and transplantation. Plastic procedures for hydronephrosis are clearly described (in German) by Bischoff and are beautifully illustrated. Hartwell Harrison's contribution (in English) on the adrenals is outstanding in providing, probably for the first time, a comprehensive and up-to-date account of the surgery of these glands. This deals not only with problems of diagnosis and localisation of adrenal tumours but also with the place of adrenalectomy in the treatment of hypertension and certain forms of malignant disease. Finally, a long section by Tönnis and Bischoff (in German) is devoted to the surgical treatment of various neurogenic disorders of the urogenital tract, including renal denervation, presacral neurectomy, and various types of sympathetic and parasympathetic blockade, as well as plastic procedures on the bladder neck.

One of the important features of the book is the quality of the illustrations, which amply support the technical descriptions in the text. It would be wrong, however, to regard the work purely as a manual of operative technique, because the scope and place of the various operations is critically reviewed and supplemented by much up-to-date statistical information. The volume fully maintains the high standard of its predecessors and is a valuable addition to the literature on operative urology.

1. See *Lancet*, 1961, i, 1267.

A Course in Epidemiology

Editor: I. I. ELKIN. Translated from the Russian by C. R. PRINGLE, PH.D. London: Pergamon Press. 1961. Pp. 518. 70*s*.

WE use "epidemiology" in two senses: specifically of a disease to describe its origin and spread in the human herd, and as a discipline per se not limited to infectious diseases and concerned as much with methods as with results. The editor of this book defines epidemiology as "concerned with the study of the origin and development of epidemics. It is devoted to discovering the causes which favour their spread and the elaboration of control measures based on scientific and practical data". Accordingly this work covers much the same ground as the admirable *Control of Communicable Diseases in Man*, published by the American Public Health Association, but at greater length.

The first part deals with general epidemiology with special reference to the administrative measures used in the U.S.S.R. It is sound but does not venture far into the theoretical and statistical foundations of the subject. The larger part deals with the infectious diseases seriatim and is by many hands. Each writes on the same general plan: history, diagnosis, bacteriology, epidemiology, personal prophylaxis, and control. Almost every chapter makes comments—perhaps unwittingly—which invite elucidation, but in general the Russians' problems are our problems and their methods of control are very similar but rather old-fashioned. Because the graphical representation of the incidence of diseases in the U.S.S.R. is based on an arbitrary zero the figures cannot be related to those in other countries. Venereal diseases are not mentioned. Some comments are very odd: "Pasteurisation does not ensure complete destruction of *Myco. tuberculosis* in milk"—just like that, without amplification.

It must be understood that this is a textbook, and it is therefore dogmatic. At the same time when alternative views are quoted it is not always easy to decide which is supposed to prevail—e.g., five rat poisons are approved but no guidance is given for choosing between them. When he has digested this book the assiduous student will know a great deal, but he may not be a very useful hygienist.

Clinical Auscultation of the Heart (2nd ed. Philadelphia and London: W. B. Saunders. 1959. Pp. 657. 77*s*.).—For the past ten years the relatively slim book by Prof. Samuel A. Levine and Dr. W. Proctor Harvey has been essential reading for the physician interested in cardiology and the keen senior medical student. The second edition has become a textbook in size, but remains readable because the authors often quote interesting examples of the value of auscultation from their vast experience. Inevitably, however, this has resulted in a great deal of irrelevance for the reader interested only in the root of the matter. The section on arrhythmias continues to be one of the most valuable, though it is weakened by the omission of observations on the venous pulse. This is not the right book for those who want a correlation between heart sounds and mur-

murs and hæmodynamics or who wish to study phonocardiography, but it makes magnificent reading for the cardiac clinician.

Treatment of Cancer and Allied Diseases (*Vol. IV.* 2nd ed. London: Pitman Medical Publishing Co. 1961. Pp. 667. 240*s.*)—This volume continues the series edited by Dr. G. T. Pack and Dr. I. M. Ariel and deals with the breast, chest, and œsophagus. It maintains the extraordinary detail and completeness which has been a notable feature throughout all earlier volumes, with emphasis on techniques, both operative and radiotherapeutic.

Virus Meningo-Encephalitis (London: J. & A. Churchill. 1961. Pp. 120. 12*s.* 6*d.*).—It is now clear that meningo-encephalitis has many causes. At this Ciba Foundation Study Group clinicians and virologists discussed the problem with special emphasis on the increasing capabilities of virus diagnostic laboratories to elucidate the cause of these diseases. For anyone concerned with these cases this is an interesting little book, showing that the questions outstanding are due partly to lack of liaison between virologist and clinician and partly to deficiencies in knowledge.

Current Therapy 1961 (Philadelphia and London: W. B. Saunders. 1961. Pp. 806. 87*s.* 6*d.*).—For the new edition this useful annual has been largely rewritten by different authors, and it is virtually a new book. The price has crept up a little, but as a comprehensive review of rapid changes in modern therapeutics this edition is as valuable as its predecessors. Its usefulness on this side of the Atlantic would be greater if more English names could be included; it seems that more and more drugs are coming to have different names in Britain and America.

New Inventions

FLUON ARTERIOVENOUS SHUNT FOR REPEATED HÆMODIALYSIS

REPEATED hæmodialysis by means of conventional cannulation techniques results in progressive destruction of peripheral vessels. In acute renal failure in cases of multiple injuries, access to peripheral vessels may be limited by tissue trauma, dressings, or amputation. In chronic intrinsic renal disease useful prolongation of life by repeated dialysis at relatively long intervals requires conservation of vessels and minimal inconvenience to the patient.

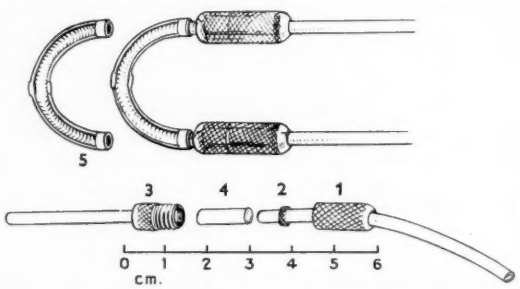
A permanent exteriorised arteriovenous fistula between a suitable peripheral artery and vein permits simple and rapid connection to the artificial kidney whenever necessary without any disturbance to the patient.

Polytetrafluoroethylene (P.T.F.E., 'Fluon', 'Teflon') is at present the most suitable material for permanent cannulation. It can be used over a wide temperature range, has excellent electrical characteristics, and in addition it does not absorb water, is resistant to almost all solvents and chemicals, and is non-toxic. Because of its properties fluon does not promote blood-clotting and can be used in the body without tissue reactions.

A technique for preparing and inserting the cannulæ has already been described by Scribner.[1] Our technique is essentially similar except that an improved type of former has been developed for heat-moulding and that the cannulæ are sterilised either by boiling after being wound with single-core copper wire covered with polyvinyl chloride (P.V.C.), or by immersion in a formalin solution if time permits. The purpose of the P.V.C.-covered wire (Radio-Spares single P.V.C. solid) is to maintain the shape of the cannulæ in the steriliser. At boiling-point the P.V.C. is softer than the fluon and does not mark it. Size 10 thin-wall fluon tubing has proved most suitable for the cannulæ. Because fluon has an extremely low coefficient of friction the task of joining the cannulæ to complete the exteriorised circulation is extremely difficult. The pattern of connector described by Scribner is based on a standard industrial Swage-lock fitting, and safety depends upon crimping of the fluon cannula by nylon washers which are compressed by a nylon cap screw into a coned sleeve. This safety is not absolute, and on one occasion in our experience the arterial cannula slipped from its retaining washers—fortunately while the patient was in hospital. To provide complete safety with greater compactness a new pattern of connector has been developed. This connector holds the two ends of fluon tubing together in a butt joint within a sleeve of the same material, thus preventing any contact between the blood and a non-fluon surface even if the butt joint is imperfectly fashioned or the tube ends separate slightly, and a positive grip is obtained by means of self-threading metal parts. As an added precaution the ends of the tubing are lightly coated with silicone grease.

1. Scribner, B. H., Buri, R., Caner, J. E. Z., Hegstrom, R., Burnell, J. M. *Trans. Amer. Soc. artificial intern. Organs*, 1960, **6**, 104.

The procedure of assembly is as follows. First, the female end-piece (see figure) is passed over the end of the cannula and the small metal collar is screwed on for a distance of about 6 mm. using a modified pinvice. The other end is prepared by screwing on the male end-piece, and the protruding end of fluon tubing is trimmed off with a sharp knife. A short sleeve (about 1·5 cm.) of size 9 fluon is passed into the annular space between the fluon tubing and the male end-piece, thus providing a socket for the cannula. The lip of the sleeve may require slight eversion by means of a blunt taper to allow insertion of the cannula, lubricated with silicone grease, until the two ends of tubing butt within the sleeve. Retention is ensured by



Edinburgh pattern of connector assembly: (1) female end-piece; (2) metal collar; (3) male end-piece; (4) sleeve of size-9 fluon; (5) metal sleeve to protect U-shaped connecting segment between arterial and venous cannulæ.

screwing the female end-piece fingertight over the male. Experience has shown that it is advisable to wipe the threads of the end-pieces with silicone grease before the final screwing-on in order to facilitate disconnection.

It has been found convenient in practice to keep the female end-pieces on the arterial and venous cannulæ and to use the male end-pieces for connection to the dialysing circuit and for the U-shaped length of fluon tubing which maintains the arteriovenous flow at other times. This U-shaped tube is protected from injury by a metal sleeve, and the whole assembly is mounted on a perspex arm-plate.

Over the past eight months this connector has proved entirely satisfactory in use.

We wish to thank Mr. R. Moncrieff for his patience in making many prototypes during the early stages of this work. The 'Fluon' tubing connectors and accessory tools may be obtained from Buccleuch Radio Manufacturers, Light Engineering Section, Bankhead Drive, Edinburgh, 11.

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Industry and Profession

THE pharmaceutical industry has the virtues of competitive private enterprise; and in the advance of medicine it has become an invaluable partner of our profession. But partnerships always have their element of strain, and many doctors are beginning to be restive under what they regard as commercial pressures. The tendency, they feel, is towards transforming useful cooperation into a rather dangerous collaboration; and this feeling has enough foundation to make all parties think again about their role and their relationship.

That the sale of drugs should be strictly separated from the treatment of patients is comparatively new: in the old days the apothecary who did general practice was shopkeeper as well as practitioner. But the principle underlying this separation was important; and now that so many drugs are expensive it is more than ever necessary that, in choosing one or other, the doctor should have no motive except his patient's benefit. The manufacturer is, of course, entitled to keep the doctor fully informed of the advantages of his various products: he is entitled to advertise to the profession. Indeed, as one of the many journals that are at present maintained partly by advertisements, we should be slow to question that right; and we have lately defended a certain freedom in its exercise.[1] But this does not mean that we think that the freedom is always being wisely used. Of late years an increasing proportion of the advertisements appearing in journals or distributed through the post have been clever rather than factual: they smack of the advertising expert rather than of the manufacturer himself, by whom most doctors would prefer to be addressed. Everybody now knows that skilful advertising can defy probabilities and sell almost anything to the public; but many of us feel that, where a serious profession is being approached on a serious subject, straightforward information is more suitable than the kind of ingenious persuasion nowadays so fashionable. The frequent repetition on which some types of persuasion rely is no substitute for reason, and it constitutes a kind of pressure which is no compliment to the professional reader.

If we ask why such pressure is applied, the answer is that, to get a sufficient return for their work, manufacturers must often induce doctors to prescribe drugs which in fact differ very little from those sold by their rivals. Because major discoveries are, at best, few and far between, most firms devote the greater part of their research to modifications and improvements; and because these, though useful in their way, seldom make much real difference to patients, they are unlikely to be widely prescribed unless a good deal of effort goes into their promotion. Some observers believe that the industry's chief need is to divert its research towards making really new discoveries; and as an inducement to this change DOWLING [2] suggests that new drugs should be allowed only one proprietary name—to be reserved for the discovering firm and any others it may license. Senator KEFAUVER proposes that, in order to get a patent, a drug must be significantly different from any other in its effects as well as in its structure.[3]

But the relationship of the industry and the profession is not only that of supplier and client. Usually, before a new drug is advertised at all, it requires clinical trial, in which doctors in hospital or general practice are asked to ascertain its effects. Such an investigation can be very valuable, and those undertaking it are actuated by the hope that it will prove so. But it is seldom easy to arrange; and besides the difficulties inherent in clinical trial there may be others of the kind described by our correspondent on p. 421. His warnings should be pondered by anyone who may want to take part in such investigation; but in fairness to drug firms we should point also to the obstacles they may have to overcome in order to get any kind of trial carried out—let alone published speedily in a professional journal. On the one hand the profession complains that drugs are often put on the market before there have been adequate inquiries—entirely independent inquiries, properly controlled, and made known to doctors through the ordinary medical journals. On the other hand, we have yet to devise a system by which the clinical testing of drugs is done regularly and satisfactorily and the results are promptly reported through professional rather than industrial channels. Objective reports objectively arrived at should be the aim of all concerned; and DOWLING [2] is right in wanting to see more young doctors " trained in the concepts and methods of drug testing " so that they may be ready for such work. But if, as he recommends, pharmaceutical firms are to provide funds for the laboratories and wards where the tests are done, they ought really to do so through an intermediary body which ensures that the people who make the test are under no sort of obligation to any one firm or even to a group of firms. Control of clinical tests should be strictly academic and judicial; for these tests are the independent professional evaluation on which doctors should decide whether or not to try the drug in their practice. Ideally, no drug ought even to be marketed unless it is worth using; but nowadays manufacturers often find themselves deciding without good enough evidence. Though they spend a great deal of money on clinical trials, much of this goes on what one may call *nonne* research—which expects the answer " yes " and can usually evoke at least " perhaps ".

The profession exists solely to do its best for patients; and its arrangements with anyone else—whether an industry or a Government—should never be such as to interfere with that function. That it should accept money from industry for the investigation of drugs and the publication of results is permissible, but only if accept-

1. *Lancet*, 1961, i, 379.

2. Dowling, H. F. *New Engl. J. Med.* 1961, **264**, 75. See also editorial, p. 97.
3. *Science*, 1961, **134**, 89.

ance in no way impairs its judicial detachment. In the *Journal of Medical Education*, Prof. CHARLES D. MAY,[4] of New York, explains how this necessary professional detachment can be threatened " by the new vogue among drug manufacturers to promote their products by assuming an aggressive role in the ' education ' of doctors ". Is it prudent, he asks, for the profession to become so largely dependent on the drug firms " for support of scientific journals and medical societies, for entertainment, and now also for a large part of their education "? Hardly any of us, perhaps, could read his trenchant and courageous article without risk of a blush somewhere. Medical journals, in particular, are very far from escaping his criticism—partly because he regards advertisements as a " financial subsidy " from the advertisers, partly because he no longer depends on these advertisements as sources of information, but also, more positively, because he believes that journals are failing to supply what the practitioner needs—up-to-date information with free and pointed criticism. Unfortunately, the medical journal is apt, he says, to be more a repository of data than an organ designed to interest and enlighten the reader; and it is the doctor's sense of frustration in using his own literature that " makes him quick to turn to the appealing ' educational ' material of the pharmaceutical concerns "—some of which is in point of fact more useful than the journals and postgraduate programmes sponsored within the profession. Advertising experts are not far wrong when they point out that their methods would be less successful if medical educators and editors did their jobs better. And the best comfort MAY can offer here is that, if we are losing the battle to dominate the doctor's habits and beliefs, it is because the sides are not fairly matched:

> " The drab and prosaic legitimate journals must limp along on relatively meager resources openly raised through paid subscriptions or stoop to sharing the promoter's bounty by carrying his advertisements, which enshroud and often conflict with the editorial text. The beautiful and exciting magazines and newspapers from industry can be given away, whatever the cost, because the expense is conveniently included in the price of products the physician is led to prescribe."

Whereas open clashes of opinion between fairly matched adversaries will eventually disclose the truth (as nearly as possible), " this process is stifled when industry can afford to make blatant use of the mass media, while the profession remains content to express its opinion softly through outlets partially stilled by a feeling of dependency on subsidy from advertisers ".

In the United States in 1959 drug companies selling their products through doctors' prescriptions are thought to have spent some 750 million dollars on promotional activities; and one cannot help wondering how much of such money—ultimately derived from patients—is usefully spent. In the last analysis, as MAY says, the purpose of this expenditure is simply to get the doctor to prescribe products of particular firms by brand names: in the companies' view, presumably, it is their only means of ensuring that enterprise and discovery are rewarded. But the techniques of modern advertising have too often converted legitimate promotion into a positive assault on the doctor's mind. Not only is he to be informed, but also—by the offer of things which are valuable or pleasant—he is to be conditioned into friendly association with particular drug-houses. The object of this type of education is in sharp contrast to the object of true education, which, as MAY defines it, is " to cultivate the use of the mind for independent judgments ". Especially disturbing, therefore, is the spread of promotional persuasion to the student, whose critical detachment of mind, created with such difficulty by his teachers, may be early sapped by various kinds of favours to himself or his school. Yet, after all, which of us, his seniors, can say that we have never attended sponsored conferences or accepted entertainment? Everywhere the line is hard to draw; for often the manufacturers are actually as interested in medicine as ourselves, and spend their money without the slightest intention to suborn us. Often we have reason to know that they have no wish to attach any strings at all to what they give. Nevertheless, with the world as it is, we should be rash to assume that even the most prosperous manufacturer supplies money habitually to medical groups or individuals without an object; and we should be very careful lest achievement of that object should lower the status of our profession or its members—young or old.

There are ample grounds, as MAY remarks, for kindly feelings between doctors and those who furnish them with invaluable remedies. But he is right in urging that, though we should cultivate cooperation, we must avoid entanglement.

4. May, C. D. *J. med. Educ.* 1961, **36**, 1. See also succeeding article (p. 24) and editorial (p. 91).

Asthma

THE effects of an antigen-antibody reaction depend largely on the site at which the reaction takes place. One factor determining the site of such a reaction is the portal of entry of the antigen. A second factor is the location in the body of the cells to which the relevant antibody is attached. For example, if the antibody is fixed in smooth-muscle tissue, spasm is the usual consequence; while if it is attached to red blood-cells hæmolysis may result. Where the antibody is widely distributed, the predominating symptom is partly conditioned by anatomical features. In the guineapig, in which the bronchial muscles are particularly well developed, the principal result is asphyxia due to bronchospasm; in the dog, where the hepatic veins are very muscular, bloody diarrhœa and circulatory collapse results from splanchnic congestion. In man there are several such " shock organs ", and the manifestations of acute anaphylaxis are varied. Bronchospasm, giant urticaria, angioneurotic œdema, or peripheral circulatory failure may occur. Production of antibody tends to be localised, and the antibodies produced tend to be fixed in nearby tissues. This is illustrated by the observations on rabbits by OAKLEY et al.,[1] who injected diphtheria toxoid into one leg and tetanus toxoid into the other. It was subsequently

1. Oakley, C. L., Batty, I., Warrack, G. H. *J. Path. Bact.* 1951, **63**, 33.

possible to extract principally diphtheria antitoxin from the tissues of the leg into which diphtheria toxoid had been injected, and principally tetanus antitoxin from the tissues of the leg which had received tetanus toxoid. In susceptible people ingested antigens tend to induce gastrointestinal allergy, inhaled antigens respiratory allergy, and contact antigens skin sensitivity. Antigens which are administered parenterally are more commonly responsible for generalised allergic responses. The disposition of antibodies depends also on the nature of the antigen, the presence of inflamed tissue (in which they tend to accumulate),[2] and hereditary factors. Some types of antibody remain free in the plasma. They can then act as blocking antibodies, reacting with antigen without causing disturbance in the tissues—a fact of fundamental therapeutic importance.

The tissue response to the combination of antigen with fixed antibody seems to be of two main types. The first of these is immediate in onset, is apparently mediated by humoral agents such as histamine, and is to a variable degree relieved by anti-histamine drugs. The second type is a delayed response, which may take up to twenty-four hours to develop, tends to be a cellular reaction rather than an acute response to pharmacologically active agents, and is in general inhibited by cortisone. The distinction is clearest in the skin, where the acute urticarial response contrasts with the cellular type of response to, for example, tuberculin or poison-ivy. Which type of reaction occurs seems to be determined by the nature of the antigen. Antigens derived from microorganisms are particularly prone to produce delayed reactions; but in practice both types of reaction can often be recognised in a single case.

These observations throw some light on the genesis of allergic asthma. SCHILD et al.[3] in 1951 showed that bronchial muscle from asthmatic patients would respond in vitro to the specific antigens to which the patients were sensitive by bronchoconstriction and histamine release, which were followed by desensitisation. This strongly suggests that the appropriate antibodies are fixed in the bronchi—a " shock organ " characteristic of the species. Anatomical abnormalities of the bronchial tree increase susceptibility to the consequences of an allergic reaction in the bronchi.[4] In the early stages of the disease, the antigens to which the bronchi are sensitive can usually be shown to be those which commonly enter the body by way of the respiratory tract: these antigens may differ from those to which the skin, for example, is sensitive,[5] confirming that the antibodies are at least partly localised in the bronchi. Asthma may develop after acute or chronic respiratory infections, raising the possibility that antibody is localised in inflamed tissue. A family history not only of allergic disease but also of asthma is common,[6] which points to a hereditary tendency for antibody to be localised in the bronchi. The hereditary tendency to asthma has been thought to be conditioned by psychological factors; but in a series of asthmatics POTELIAKHOFF [7] could find no uniform grouping of abnormal personality traits, other than susceptibility to stress situations. The generation of relevant antibodies which remain in the plasma has been demonstrated in allergic asthma.[8]

Antigens provoking attacks of asthma often clearly gain access via the respiratory tract. Both immediate and delayed reactions can be demonstrated. The immediate type of response is evinced by mild attacks induced by inhalation of antigens to which the patient is sensitive; and such attacks can sometimes be inhibited by anti-histamine drugs.[9] Delayed reactions may take place up to twenty-four hours after inhalation of antigen; these are more usual in patients sensitive to dust extracts, and are particularly susceptible to supression by cortisone.[10] Thus bronchial asthma has all the properties of a typical allergic disease. These are of course modified in older patients and in chronic asthmatics by sensitisation to multiple antigens, by the sequelæ of acute or chronic infection, and by structural changes in the lung. But the basic disease process is the abnormal tendency for antibodies to inhaled antigens to be produced and for these to be localised in the lungs.

Two mechanisms have been suggested to explain the desensitising effects of increasing small doses of a specific antigen: first, that blocking antibodies are produced and react with exogenous antigen without producing organic effects; secondly, that small amounts of antigen neutralise the fixed antibody in the shock organ, a little at a time, without producing a major tissue reaction at any stage. Parenteral administration of the desensitising agent might be best suited to the first of these mechanisms: local application to the second. MCALLEN [11] has compared the effects of desensitisation by subcutaneous and inhalation routes in 100 asthmatics selected for their response by asthmatic attacks to inhaled house-dust or pollen antigens. The course of the desensitisation was monitored by measuring the sensitivity of the bronchi to minute amounts of inhaled antigen, bronchial reactions being assessed by means of the vital capacity. Pollen-sensitive patients developed increased bronchial tolerance to antigen when they were treated by either route. Dust-sensitive patients improved objectively only when treated by the bronchial route. This seems to suggest that the production of blocking antibody by systemic administration may be more important in pollen than in dust sensitivity. The difference was not related to the presence or absence of delayed reactions as a feature of the response, since the two groups were well matched for numbers of " late reactors ".

This work confirms that improved bronchial tolerance to inhaled antigens can sometimes be generated by desensitisation. But the disadvantages of desensitisation —that it is time-consuming and suitable for only some patients, and that its effects are transient—are as prominent as in other allergic diseases. At present

2. Miles, A. A., Miles, E. M. *Brit. J. exp. Path.* 1943, **24**, 95.
3. Schild, H. O., Hawkins, D. F., Mongar, J. L., Herxheimer, H. *Lancet*, 1951, ii, 376.
4. Williams, E. O., Williams, G. E. O. *Brit. med. J.* 1949, ii, 897.
5. Herxheimer, H. *Int. Arch. Allergy*, 1951, **2**, 40.
6. Williams, D. A. *in* International Textbook of Allergy (edited by J. M. Jamar). Oxford, 1959.
7. Poteliakhoff, A. *Med. Wld, Lond.* 1958, **89**, 315.
8. Kallós, P., Kallós-Deffner, L. *Int. Arch. Allergy*, 1951, **2**, 70.
9. Herxheimer, H. *Brit. med. J.* 1949, ii, 901.
10. Herxheimer, H. *ibid.* 1954, i, 184.
11. McAllen, M. *Thorax*, 1961, **16**, 30.

" bronchial hyposensitisation " seems unlikely to prove more than a hobby for the enthusiast and a research tool. The treatment of bronchial asthma remains mainly symptomatic.

Teaching of Everyday Psychiatry

". . . to train the student for good medical practice it is not sufficient to teach him only a large amount of impersonal facts and techniques; it is just as necessary to give him at the same time an opportunity for learning how to establish and maintain a personal relationship with his patients, and how to deal with the emotional problems that contribute to their being ill."

We entirely agree. And that is why we have printed the series of articles concluded by Professor STENGEL this week. By a happy chance the World Health Organisation has chosen this moment to produce a fuller and larger series[1], introduced by Dr. E. E. KRAPF in an essay including the words quoted above. The casual reader may be tempted to dismiss the subject, on the ground that psychiatry is just another specialty—and everyone knows that every kind of specialist is always asking for more of the student's time. But this will not really do. Psychiatry is indeed a specialty, and, as in other specialties, the student will have to be taught " to what extent he is competent to deal with the problems he encounters, what solutions can be provided by the fully trained worker, and in what ways he can assure his patient of proper assistance at the proper time ". But, as Dr. KRAPF goes on to say, this specialised goal is " completely overshadowed by the general one of teaching the medical student the salient facts of ' behavioural science ', which must form the basis for the competent handling of the ' human factor ' by the physician ". How much more efficient and satisfactory the work of the practitioner will be (he adds) " if he is able to treat persons instead of diseased organs ".

The same thought is put by Dr. S. LEBOVICI when, in setting out the reasons for teaching medical sociology and psychology to medical students, he puts first the need that " the physician, accustomed to the anatomo-clinical method successful in nineteenth-century medicine, must again learn to consider each patient as a person ". On the other hand, as Prof. TSUNG-YI LIN remarks, this need may be less in countries where medical practice is traditionally personal in character. He quotes SINCLAIR [2] as saying that, whereas in the United States the emphasis is on the scientific nature of the medical curriculum, in Britain it is on the healing of the sick rather than on advancement of methods of healing them. And he also quotes CURRAN'S [3] view that teaching of the humanistic approach should be the responsibility not particularly of psychiatrists but of the rest of the teachers who have closer contact with students in the general clinical setting. Prof. FERGUSON RODGER, in his contribution to the W.H.O. discussion, says that the strong tendency in Britain towards a personal and humanistic approach—which has been criticised on the ground that it turns out good practitioners but poor scientists—makes it hard for British psychiatrists " to assume the role of mentor and instructor in all matters pertaining to the doctor-patient relationship ". He points out, too, that the progress made by psychiatry as a part of medical education should not be judged solely by the number of hours allotted it: one must also take account of other signs, such as a more favourable attitude of other teachers to the psychiatric point of view. " It can be argued that the ultimate indication of success in incorporating ' mental health ' teaching in the curriculum would be the disappearance of the psychiatrist as a teacher except in his specialized role as an instructor in the techniques of psychotherapy and in the diagnosis and treatment of psychiatric disorders. This state of affairs can be achieved by making the collaboration of the psychiatrist with his colleagues as close as possible, not only in teaching but also in treatment, diagnosis, and research in the wards of the teaching hospital."

The report includes a survey, by W.H.O.'s mental-health unit at Geneva, of the teaching of psychiatry in various countries. The notable variety, not only in extent but also in scope and method, can be traced to a basic disagreement on the purpose of the training:

" The curriculum of some schools appears to be devised merely to enable the future general practitioner to recognize the odd psychotic he may come across in his practice. In others, the emphasis is mainly on ' teaching ' a good doctor-patient relationship. Elsewhere, psychiatry is considered as an ingredient in a ' total ' approach to medicine. It is with these basic issues that any discussion of the undergraduate teaching of psychiatry must start."

Whatever their views on these issues, medical teachers should give heed, we think, to Prof. E. S. TURRELL'S remarks on the readaptations and readjustments required of the student in turning himself from a lay student into trained doctor. Both intellect and emotions are strained in mastering increasingly complex scientific concepts and at the same time weathering the transition between, on the one hand, his pre-existing lay prohibitions and inhibitions, and, on the other, the role and characteristics of a physician:

" Most medical students are reared in the cultural and social environment of the middle or upper middle class of the society in which they live. Throughout his life the student has been subjected to the usual prohibitions and inhibitions of his curiosity concerning sex and other physiological and anatomical functions. During the process of medical education, he is required to overcome these prohibitions and inhibitions in order to learn about the anatomical construction and physiological functions of the human being. He is required to dissect a dead body, though previously taught to respect and revere the dead. He must examine and study excreta that he has been taught in the past to view with disgust and repugnance. He must learn to peer into all of the orifices of the human being, to examine the most private areas of men, women and children, and yet, in some way, master his

1. Teaching of Psychiatry and Mental Health. World Health Organisation: public health papers, no. 9, 1961. Obtainable from H.M. Stationery Office at 10s. Pp. 186.
2. Sinclair, D. C. Medical Students and Medical Sciences. Oxford, 1955.
3. Curran, D. *Brit. med. J.* 1955, ii, 515

own aroused feelings. He must form relationships with patients, see them die, and go on without letting his sorrow interfere with his care of the next patient. He must witness, and assist in, the surgical repair and removal of many organs of the human body without allowing his own feelings about the procedure or the patient to interfere with what he is doing. He learns that it is difficult to be 'helpful', that wished-for gratitude from patients is not always forthcoming, and that avoidance of malpractice suits may be of greater concern to some physicians than the patient's response to treatment. He may encounter man's inhumanity to man and yet must not allow his own feelings to interfere with his care of the patient, whether the patient is the injured or the aggressor."

It is doubtful, Professor TURRELL says, whether medical schools pay enough attention to the emotional problems of this transition.

Two further quotations must suffice. LEBOVICI seems to us right when he says that (quite apart from medical psychotherapy as now practised) a psychotherapeutic attitude "should underlie the doctor's actions and should be inculcated in the medical student from the beginning of hospital work." And Prof. O. V. KERBIKOV does well to recall a remark, long ago, by a man who was once a dispensary physician. "If I were a lecturer," said CHEKHOV, "I would try to draw my audience as deeply as possible into study of the subjective feelings of the patient, and I think that this would really be of use to the students."

Annotations

THE PROSPECTIVE LABORATORY

EVERYONE who has had a hand in designing a laboratory will admit that he could probably do better next time. The amateur knows nothing about methods or materials, the professional not much more about the function of the building. Only too often the relative space allotted to working benches offices, cleaning, and storage is more or less a guess based on preconceived ideas and on second-hand experience. Should there be one large or several small laboratory units? How wide should benches be? How many sinks and fume cupboards are needed? All these questions are as difficult for the professional architect as for the prospective user. In 1954 the Agricultural Research Council, planning to build some new institutes for research, invited the help of the Nuffield Foundation's Division of Architectural Studies in providing definite answers to some of these problems. The report of this investigation which has now been published, is a most convincing document.[1]

The essential furniture of the laboratory is the working bench; and the first step was to discover, by repeated observations in many kinds of laboratories, what length of bench the average worker uses. The "average worker" is admittedly a figment, but the combined results of many thousands of observations on eleven branches of science give surprisingly consistent results. Biochemists are the most greedy of space and botanists the most modest, but a 15-foot run of bench will satisfy most scientists for most of the time. Three workers in a team do not require 45 feet but about half that length. The same methods were applied to the demand for sinks, fume cupboards, and writing space. Plant physiologists spend 44% of their working day in reading and writing, but pathologists can spare only 25%. This method of study presumes ideally diligent workers, and no account is taken of time spent looking out of the window or hunting for apparatus borrowed by a colleague; but we see no reason to doubt the general truth of the conclusions.

The width of a bench, clearly, is decided by the length of the human arm. This report suggests 24 in., but perhaps this is too narrow: the back of the bench, even if out of reach, is a useful place for a bottle or a tool which is wanted only once an hour. The height of benches was the subject of an inquiry by the British Standards Institution and the suggestions are reasonable. The crux of the matter is the relative time spent standing and sitting, and in many laboratories it is worth having a run of bench 28 in. high for microscopy with the remainder at 36 in. For most people the right height is the one to which they are accustomed. Perhaps this report does not make enough of the minimum depth beneath the bench: there are few things so uncomfortable as the bench strengthened in front by a web which chafes the anterior surface of the thighs.

A problem which affects the shape of the whole building is the size and proportions of the individual laboratory unit. A 40-foot run of bench (including sinks and fume cupboards) is enough for two or three workers. This can be housed most economically in a room about 20 ft. × 12 ft. with the long axis at right-angles to the outer walls and with benches on the long sides only. A square room with the same length of benching wastes floor space and has at least two corners useful only for the accumulation of rubbish. It is true that the long room cannot rely on natural lighting, but this report devotes a lot of space to the lighting of rooms of all sorts and to the engineering services. Each ancillary room presents the architect with its own problems. Centrifuges create, and balances must be protected from, vibration. Rooms to be kept at a constant temperature must be sited so that they are not exposed to the fluctuations of the outside air. Deep freezes are most satisfactory if housed in a larger cold room. Washing, sterilising, and media-making are most economical of labour and time if there is a linear flow of glassware from "infected and dirty" to "clean and sterile"; but unfortunately the methods of work study used in the early parts of this report were not applied to these mundane processes. There is no guidance on the area of cleaning room in relation to the total size of the institution, and in our experience this is almost always underestimated. The sections on sterilisation and on the animal-house give evidence of wide reading rather than much practical experience.

The report will be a valuable guide for those who have to design new laboratories in hospitals; but its subject (we must emphasise) is laboratories for *research*. The hospital pathologist must have rooms for patients and a large office; he will certainly make much use of the telephone; and he may have to house a blood bank or a central sterile supply. We very much hope that the Nuffield Foundation will be able to apply the methods used in this inquiry to the problems of the hospital laboratory. Indeed in the design of hospitals as a whole there is still too much guesswork.

1. The Design of Research Laboratories. The Division of Architectural Studies of the Nuffield Foundation. London: Oxford University Press. 1961. Pp. 211. 45s.

TREATMENT OF THROMBOANGIITIS OBLITERANS

ONE of the oddest facets of modern medicine is the imperfect communication between English- and French-speaking workers. This division has led to differing attitudes and emphasis; and facts that on one side of the Channel are taken as self-evident are not accepted on the other. This is well exemplified by the discrepant approaches to vascular physiopathology and surgery. Following Leriche's lead, many Continental workers are convinced of the dominant importance of vascular spasm and of the value in treatment of arterectomy and of adrenal extirpation—ideas that are alien to most British workers.

In a Moynihan lecture [1] Professor Orban, of Liége, a disciple of Leriche and a valued friend of many British surgeons, discussed thromboangiitis obliterans (Buerger's disease)—which he would prefer to call thromboangeiosis. This, he claims, is not an inflammatory process: it should, instead, be regarded as an arterial thrombosis which causes intimal stratification, leaving the media, elastica, and adventitia unchanged. The thrombus undergoes fibrinoplastic metaplasia; signs of inflammation and giant-cell systems are found only when sepsis has become established distally. In the initial stage of the intra-arterial lesion it is histologically impossible to differentiate the picture of thrombosis in thromboangiitis from that of post-traumatic or a postembolic thrombosis.

That endothelial changes are widespread even in very early cases is suggested by the case of a man of 37 who presented solely with pulp gangrene of one finger due to digital-artery thrombosis. He died accidentally three weeks after the onset, and intimal proliferation was found in the brain, bronchi, mesentery, and limbs. If this case can be classified as thromboangiitis (and on the evidence presented this certainly cannot be excluded) then it is evidently to be regarded as a disseminated vascular disease, rather than a peripheral one. But can we in fact regard endothelial proliferation as characteristic of thromboangiitis—in the absence of embolism and trauma? The answer is probably No: it is a common enough change in a wide variety of diseases, notably of the " collagen " group.

Leriche laid great emphasis on the importance of adrenal dysfunction in the ætiology of thromboangiitis obliterans. Fontaine [2] claimed that in 75% of cases distinct adrenal-cortical changes were detectable; and others have reported similar findings. In Orban's 13 personal cases of adrenalectomy for thromboangiitis obliterans, the findings fit closely the pattern of those previously described, with hyperplasia of the fasciculata and wearing down of the glomerulosa, noticeable enlargement of the fasciculata which is made up of spongiocytes full of lipoid, and, in many cases, pseudoadenomas. The reticularis does not show any perceptible histological change. How specific these changes are may be doubted, since comparable findings have been revealed in atherosclerosis. Can the adrenal picture be linked with the arterial lesions? Orban says that spasm of the peripheral vessels in thromboangiitis is undisputed; and he cites examples of spasm demonstrated by arteriography and relaxed by sympathectomy and arterectomy. It has been shown that mineralocorticoids given in excess can cause the classical arterial lesions in animals, and that the corticosteroids sensitise vessels to the action of adrenaline. Therefore removal of the adrenal overactivity or dysfunction will eliminate the spasm, which untreated leads to thrombosis and endothelial reaction. The physiopathological evidence for this concept may be open to other interpretations; but the empirical evidence for adrenalectomy in the treatment of thromboangiitis is noteworthy.

The full programme, which all patients are urged to undergo at the first signs of the disease, is as follows: bilateral subtotal adrenalectomy, leaving only 0·5 g. of adrenal on the right side, plus extensive sympathectomy of four limbs. Orban believes that it is advisable to stage the operations, but to complete the series in a short period of, say, eight to ten months. His results are impressive. None of the 13 patients has had further gangrene; no amputation has been required; acrospasm and pain have gone; and ulceration has healed within a few weeks. 7 have been relieved of claudication; none have rest pain. All have put on weight, and 9 have returned to their previous occupations. The follow-up period has been short; the 1st patient was operated on in 1949, but most have been treated in the past two or three years. Orban is commendably modest and factual about the results. Even if the basis of the operation is foreign to our conceptions (or misconceptions), can the reputed therapeutic benefits be ignored in this disease, which can be devastatingly progressive in young males?

1. Orban, F. *Ann. R. Coll. Surg. Engl.* 1961, **28**, 69.
2. Fontaine, R. La chirurgie des surrinales. Paris, 1950.

SUTURES AND INCISIONS

OUR knowledge of factors in the healing of wounds has expanded notably [1]; but with regard to the effects of different types of suture material, the intensive studies of the past twenty years [2] have mainly explained in detail the basic teachings of forty years ago.[3] These details, from experimental studies, are well summarised by Wiancko et al.[4]:

Plain catgut sutures cause early, long-continued, and severe exudation often associated with damage to or even death of the surrounding tissues, abscess formation, and delay in fibrosis, which seldom develops in less than a week. The gut is rapidly absorbed, and the wound loses all tensile strength in five to six days and can be disrupted for up to nine days. The knots easily slip after imbibition of fluid, and the suture cuts out very easily because of the tissue reaction and softening produced.

Chromicised catgut sutures behave like non-absorbable sutures until the chromium disappears, and then there is a sudden increase of exudation and tissue disruption with corresponding loss of effective tensile strength and delay in fibrosis.

Silk and cotton sutures induce much less exudation and tissue destruction, and fibrosis and repair occur correspondingly sooner: the non-absorbable strands of material are separated by the same reaction, and this undergoes fibrosis with giant-cell formation. Although there is a lag period of three (silk) or four (cotton) days, the tensile strengths are much greater than with plain catgut, and wounds cannot be disrupted after the sixth day.

Wire and synthetic (*e.g.*, *nylon*) sutures excite very little tissue exudation and destruction, and fibrosis follows early and firmly, with no disruption after the sixth day. With these materials the big disadvantage is the tendency for the knot to slip. In abdominal wounds, Anglem and Gray [5] found that stainless-steel retention sutures, with the skin edges protected by

1. See *Lancet*, 1958, ii, 1110, 1165; *ibid.* 1960, ii, 248.
2. Localio, S. A., Casale, W., Hinton, J. W. *Surg. Gynec. Obstet.* 1943, **77**, 243, 376, 481. Madsen, E. T. *ibid.* 1953, **97**, 73, 439; *ibid.* 1958, **106**, 216. Postelthwait, R. W., Schaube, J. F., Dillon, M. L., Morgan, J. *ibid.* 1959, **108**, 555.
3. e.g., Rose and Carless' Manual of Surgery; 10th ed. pp. 250, 289, 324. London, 1920.
4. Wiancko, K. B., Kling, S., MacKenzie, W. C. *Canad. med. Ass. J.* 1961, **84**, 254.
5. Anglem, T. J., Gray, E. B., Jr. *J. Amer. med. Ass.* 1961, **176**, 85.

rubber or plastic " boots ", were very helpful in preventing dehiscence.

As to deep sutures, Catchpole and Winn [6] found that in dogs synthetic fibres retained their tensile strength longer than natural fibres. In man reactions to suture material are extremely varied: with catgut, while exudation should lead in the abdomen to fibrosis and adhesions in the peritoneal cavity, there are numerous exceptions.

Experimental transverse abdominal incisions have been found to heal more firmly than longitudinal incisions; but the longitudinal incisions were made through the linea alba of the rat, and so the results are not comparable with those of paramedian incisions in man. For the direction of incision, ease of access and exposure of operating area must be considered [5] besides the strength with which the wound heals. The experimental observation that post-operative abdominal support decreases the tensile strength of wounds suggests that abdominal binders should be applied only in special cases.

HOSPITAL DRUG COSTS

EXPENDITURE in the hospital service on drugs and dressings continues to rise. In a memorandum to hospital authorities [7] the Minister of Health, while admitting that some increase is necessary, urges that reasonable economy be applied. He points out that expenditure in some hospitals is much higher than seems justifiable on a comparison with that in other hospitals of similar type. Hospital authorities are urged to look into these differences and to scan the estimates of hospitals with exceptionally high expenditure before giving their approval—a procedure which he himself will adopt with the teaching hospitals.

The memorandum suggests that the following basic arrangements are essential for satisfactory control of drug expenditure:

1. Each hospital management committee and board of governors should make one of its standing committees, with strong professional representation, responsible for regularly reviewing all factors which affect expenditure on drugs and dressings and advising on action to be taken.

2. Every medical staff advisory committee should regularly review prescribing costs and receive all data necessary to enable them to do this.

3. The regional pharmaceutical committee should arrange regular exchanges of views and information with the standing committees of the hospital management committees and boards of governors.

Most hospitals now have some form of pharmaceutical committee which meets regularly and discusses the use and cost of drugs; and these committees strongly support pharmacists in controlling the prescription of expensive drugs and in discussing and applying policies on the economical use of medicaments. Meetings of such committees with newly appointed house-officers can be a valuable means of inculcating good prescribing habits.

Discussing supplies, the Minister points to the advantages of joint purchasing, and asks boards and committees to make sure that no item to which this method could be applied to advantage is overlooked. Many regional hospital pharmaceutical committees and the London Teaching Hospital Pharmacists' Committee have already organised extensive schemes and have made considerable savings. It was as a result of the action of such committees and of individual pharmacists in purchasing cheaper drugs from Continental sources that the Minister recently decided to invite tenders for branded drugs from such sources as well as from British firms and British subsidiaries of American firms, and, if necessary, to make test cases to decide the amount of royalties which it would be fair to pay. The memorandum recommends that hospital pharmacists should themselves make preparations such as infusion fluids whenever this is safe and would save money. Many pharmacists have, of course, done this for years. By agreement between hospitals, production units of sufficient size to be economical can be arranged. Very substantial saving can be achieved in this way, and the equipment needed can soon pay for itself.

Analysis of costing is recommended. Obviously costing schemes must not be so complex that they cost more than they save. Full costing would be prohibitively expensive; and the Ministry intends to issue a simple form of analysis, suitable for larger hospitals, which will not be too costly to maintain.

As regards prescribing, the memorandum points out that the advice by the Standing Joint Committee that the general practitioner need not normally go outside preparations listed in the official publications (*B.P.*, *B.P.C.*, and *B.N.F.*) and may be called upon to justify his action in doing so if the cost of his prescribing is under examination, " has its application to hospital prescribing ". This perhaps is not generally appreciated. Hospitals are advised to issue periodical bulletins on comparative costs of drugs. Many hospitals already do this and find that it brings home forcibly to prescribers the cost of many modern drugs.

A more controversial suggestion is that indiscriminate visits to junior doctors by representatives of pharmaceutical firms may cause unnecessarily expensive prescribing: " Boards of Governors and Hospital Management Committees should consult the medical staff about the extent to which access to their hospitals by these representatives should be permitted." The better firms, which are usually those producing the more important medicaments, seldom exert unfair pressure in this way; but some, usually those which are merely formulators, do make strenuous efforts to get their products into hospitals by this means. The best defence against undue sales pressure is by educating the medical student in sound prescribing habits.

The memorandum suggests that in recommending drugs for the patient's general practitioner to prescribe, cost be considered; and that the amount of drugs supplied to outpatients should be limited. There is an increasing tendency for drugs to be prescribed for longer periods than was the custom a few years ago. Then the usual limit was four weeks' supply; now three months' and six months' supplies are commonly ordered. This may be done in order to limit the prescription charges for the patient; but hospital pharmacists are sometimes appalled to find expensive drugs being merely wasted. The practice of "substitution" by the hospital pharmacists of less expensive drugs of equivalent therapeutic effect is approved, subject to proper safeguards; and this recognition of a common practice is welcome. The final recommendations are that new drugs or new brands of drugs should be introduced into a hospital only by a senior doctor, and that a senior member of the medical staff should control clinical trials. Hospital pharmacists will strongly endorse the recommendation that the pharmacist should be informed of any drugs which are to be supplied otherwise than through him.

6. Catchpole, B. M., Winn, S. A. *Lancet*, 1960, ii, 236.
7. H.M. (61) 78.

Teaching of Everyday Psychiatry *

THE SHEFFIELD PLAN

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THE teaching of psychiatry has become one of the most urgent problems of medical education. The World Health Organisation think it so important that they invited an expert committee to review the present state of psychiatric teaching and make recommendations for its minimum requirements.[1] In fact, we are witnessing something like a revolt against a gross deficiency of medical education. This revolt started in the United States and is now making itself felt in this country.

In the British medical schools the claims of psychiatry for students' time are being met to various degrees and in different ways. No two psychiatric courses are alike. Their design depends at least as much on difficulties in the rearrangement of the curriculum as on the approach of the individual teachers of psychiatry. So far hardly any of the psychiatric courses in British universities has fulfilled the minimum requirements recommended in the W.H.O. report.

Garmany and Whiteley,[2] in the first article of this series, referred to the British Medical Students' Association's (B.M.S.A.) survey [3] on the teaching of psychiatry and the unqualified approval given by the students to what they called the Sheffield Plan—i.e., the programme of psychiatric teaching in the new curriculum of the Sheffield Medical School. Since the publication of the B.M.S.A. report, the Sheffield Plan has undergone some modifications. Like other teaching programmes, it is experimental and will no doubt be modified in the light of experience.

The principles underlying the Sheffield Plan are:

1. There should be a preclinical course in psychology side by side with anatomy and physiology, with special consideration of those aspects which are relevant for the medical student. Such a course will provide basic knowledge essential for the study of abnormal behaviour.

2. The ubiquity of psychological and psychiatric problems in all fields of medical work is to be brought home to the student, by the psychiatrist, throughout the clinical part of the curriculum.

THE PRECLINICAL COURSE ON HUMAN BEHAVIOUR

A course on normal behaviour will be given throughout the second year and during the first term of the third year. For about half the medical students the second year of the curriculum is the first year in the university. Hitherto the Sheffield students have had only a ten hours' course in psychology, given by non-medical psychologists during the first term of the third year. In future there will be altogether forty sessions of one hour, spread over four terms. The course will open with two introductory lectures, one by the professor of psychology and one by the professor of psychiatry. It will fall to the latter, and his colleagues, to present those aspects of normal human behaviour which have been elucidated through the study of the abnormal. Following on the two introductory lectures, parts of general and especially of experimental psychology will be presented by a psychologist, most of it by the lecturer in clinical psychology in the department of psychiatry. A provisional list of subjects drawn up with Prof. H. Kay includes ethology (i.e., innate behaviour patterns in animals), perception, maturation, learning, memory, forgetting, individual differences, intelligence, personality, and mental testing.

The next part of the course will be concerned with physiological psychology and will as far as possible be correlated with the study of anatomy and physiology of the nervous system. It will include subjects such as the role of conditioned reflexes in behaviour, instincts, consciousness, and language and its development.

The third part will be concerned with motivations and with basic principles of psychodynamics. There will be two to three lectures on human sexual behaviour. Social psychology and certain aspects of social anthropology, with special consideration of the doctor's work, will also be discussed.

The fourth part of the course (first term of the third year) will lead the student into psychological medicine. It will, if possible, be held in a hospital lecture theatre. Among the subjects to be discussed will be psychosomatic interactions, simple anomalies from the borderland between the normal and the abnormal, and attitudes to physical and mental illness.

Throughout the course, participation by students will be encouraged and there will be as little formal lecturing as possible. Films, tape recordings, experiments, and demonstrations on normal subjects and patients will be used. The course will be flexible and no attempt will be made to cover the whole field.

During the last few years the student has had to answer one of two questions on psychology in the Physiology paper. These questions were set and marked by the psychologist. The level of the answers has been surprisingly high. The form the psychology examination will take in the new curriculum has not been decided yet.

PSYCHIATRY IN THE CLINICAL PART OF THE CURRICULUM

Having emerged from his preclinical studies, the student attends a series of introductory lectures one of which is held by the psychiatrist.

4th year.—In the first term there will be one weekly lecture demonstration on basic general psychiatry. This course is an introduction to the neuropsychiatric clerkship (four weeks) during which the student is to learn about psychiatric history taking, the doctor-patient relationship, and some elementary symptomatology. He spends six half-days in the psychiatric department, and four half-days in the nearby neurological department of the teaching hospital.

Two seminars on social psychiatry form part of a one month's clerkship in social medicine. Psychiatric casework with group discussion is included among the various features of that course, which is under the direction of the professor of preventive medicine and public health.

The student also participates in psychiatric rounds in the medical wards during his three months as junior medical clerk. On those rounds, which are attended by groups of up to six students, psychiatric aspects arising in the medical ward, including the psychosomatic

*A series of articles on the needs of students and practitioners, and how they may be met.

1. Undergraduate Teaching of Psychiatry and Mental Health Promotion. *World Hlth Org. tech. Rep. Ser.*, 1961, **208**. Some of the papers presented to the expert committee have been published as a separate volume (Teaching of Psychiatry and Mental Health: W.H.O. public health papers, no. 9, 1961). Among these papers is one by Prof. T. F. Rodger, of Glasgow, entitled The Place of Psychiatry in the Medical Curriculum —a British Viewpoint.
2. Garmany, G., Whiteley, J. S. *Lancet*, 1961, ii, 38.
3. British Medical Students' Association: Report on the Teaching of Psychiatry and Psychosomatic Medicine, 1959.

approach, suicidal attempts, and dementia, are discussed on an elementary level. The total number of such rounds for each group of junior students will be three to six.

5th year.—The psychological aspects of child development and of behaviour disorders in childhood are taught by the pædiatrician and the child psychiatrist in the course on pædiatrics, which includes a three months' clerkship in the children's department.

The psychiatrist contributes two lectures to the course in obstetrics and gynæcology. They deal with psychiatric aspects of childbearing, and of gynæcological illness.

6th year.—During the first and second term there will be one weekly lecture demonstration in psychiatry, with special emphasis on the psychoses and on mental subnormality. There is an additional weekly psychiatric session of an hour and a half during one term. While the lecture demonstrations are given to the whole class, only half their number will attend the afternoon sessions, which are to be spent in the mental hospital and in the psychiatric outpatient department. Psychiatric treatment will be discussed throughout the sixth year whenever the occasion arises. The student will also learn about the contribution of clinical psychology to psychiatry.

In their three months' senior medical clerkship the students will take part in four to six psychiatric rounds in the medical ward.

PSYCHIATRY IN THE FINAL EXAMINATION

Until now there has been one obligatory psychiatric question in the Medicine paper. This question was set and marked by the psychiatrist. In the new curriculum psychiatry will be included in the written as well as the clinical examination in Medicine; but details have still to be decided.

OBJECTS

The teaching programme outlined above should be looked upon as an experiment in cooperation. Most of the clinical part has already been implemented during the last four years. Although the programme looks formidable, the total number of hours the student spends with the psychiatrist during the 10 terms of his clinical course is not more than 70–80, not including the clerkship. The latter is probably the weakest part of the Sheffield Plan. It is too short to enable the student to observe a patient's progress over a reasonable period. It is hoped that this and other shortcomings of the Sheffield course will be remedied before long. The Rochester Scheme,[4] which is in most respects superior to the Sheffield Plan, includes a senior as well as a junior clerkship in psychiatry.

The Sheffield Plan differs from most other comparable courses in that psychiatric teaching is spread out, though rather thinly, over the whole of the curriculum. It may be criticised on the grounds that the student does not hear or see enough of psychiatry proper. Experience should help to find a reasonable balance between the various functions of psychiatric teaching.

Occasionally the question is raised whether it is right for the psychiatric aspects of medical conditions to be taught by anybody else but the physician in charge of the patients. In most cases this happens, or ought to happen, anyway. By highlighting those aspects in some cases, the psychiatrist adds to the dimensions of the student's education. Whether we like it or not, the general physician who is equally competent to teach, and to examine, on all aspects of medicine, including psychiatry, is a figure of the past, dear though this figure is to the older generation of physicians. In the final event, the integration of the various approaches presented by different teachers has to be left to the student. The success of any programme of medical education depends on whether it facilitates or inhibits this mental process.

4. Kehoe, M. *Lancet*, 1961, ii, 145.

It is hoped that the preclinical course in psychology will create respect for and a general scientific interest in what is peculiarly human in the patient. At the same time, the student will learn a great deal about himself in this preclinical course. After this preparation, his attitude towards abnormal behaviour should be more serious and mature than it used to be among previous generations of students. There are no doubt other and better methods of teaching psychology to medical students than the course outlined above. Dr. Barton Hall and Mr. R. R. Hetherington of the department of studies in psychological medicine in the University of Liverpool are going to teach normal psychology by lectures as well as seminars in a course of 60 hours. There has been some progress since Prof. L. S. Hearnshaw [5] of Liverpool presented a survey on this subject to the British Psychological Society. He advocated a close collaboration between medical and non-medical psychologists. It has been possible to adopt this policy in Sheffield, thanks to the generous cooperation of Prof. H. Kay and his colleagues in the department of psychology.

The place of psychiatry in the professional examinations is a controversial issue, although it is now generally accepted, at least in principle, that an obligatory examination in this subject is essential. Many teachers of psychiatry advocate an independent examination similar to those in other important clinical subjects. In Sheffield an alternative arrangement has been decided upon and it is hoped that it will work satisfactorily.

The Sheffield Plan owes a great deal to Prof. Stuart-Harris, who invited me first to do regular rounds in his department of medicine and encouraged the development of the clinical teaching programme, and to Prof. Smyth for his support with the preclinical course. I am greatly indebted to Dr. McCrie, the dean of the medical faculty, and to all colleagues without whose help and cooperation this scheme could not have been developed.

Occasional Book

The Doctor's English

ON a subject that can beguile its more ardent students into pedantry, Dr. Ffrangcon Roberts has produced, somewhat after the fashion of Sir Ernest Gowers, an excellent Plain Words for Doctors.[6] He points to the road from obscurity to clarity, from too many words to just enough, in a way that medical writers (and the readers for whom they write) will welcome and applaud. He does so without strict censure, and he never scores too unkindly off the miscreant writers and editors he quotes (of course, we are glad to say, anonymously). In fact, after " scrutiny of the issues of several journals published in the United Kingdom in the last two or three years ", he compliments the profession on its literary standard; and he is generally more cheerful than Sir George Pickering (who was almost despondent in the lecture we published the other day [7]) and other commentators who have mourned a lapse in the ease and clarity of scientific communication.

5. Hearnshaw, L. S. *Bull. Brit. Psychol. Soc.* 1959, p. 37.
6. Good English for Medical Writers. By FFRANGCON ROBERTS, M.D., F.F.R. London: Heinemann Medical Books. 1960. Pp. 179. 17*s.* 6*d.*
7. *Lancet*, July 15, 1961, p. 115.

We nearly—but not quite—resisted quoting this passage:

> " The opinion I have formed is that the standard, though naturally not uniformly reaching that of the best exponents of English, is one of which the profession has every reason to be proud, especially since the content is often highly technical and the meaning not easy to express. Without access to the original scripts it is impossible to determine in what proportion credit should be shared between editors and authors, but I suspect that it is the editors who are mainly responsible."

Though we fear Dr. Ffrangcon Roberts may not have been thinking too closely of *The Lancet*, we can say that many of the papers we are unable to publish (because there is only one issue a week) do much credit to their authors' command of language. It may be possible to suggest ways of setting out an article or a letter more succinctly, but the meaning of those who write to us (often in a language other than their own) is seldom in doubt. Nevertheless, we hope they will read this book!

The neologism evokes more heat in arguments about medical literacy than any points of grammar, style, or syntax. Or so it seems from the letters we receive. We have explained [3] why we at present impose no sharp censorship on new words in this journal: to do so seems to deny contributors a proving-ground for their more reasonable novelties. And Dr. Ffrangcon Roberts is at least partly with us here—and we with him when he condemns such curiosities as neanirosis (sexual desire for young girls) and ectromelus (absence of whole or part of limb or limbs). The usefulness is all: if a new word repeatedly saves time, let it be used; for example, unlike some defenders of the language, Dr. Ffrangcon Roberts would allow " kaliuresis " as an economical necessity in circumstances when " excessive excretion of potassium " would be tedious.

There is the broad matter of writing plainly (to which this book is an admirable guide), and there is the more limited and vexatious topic of the medical vocabulary and its imperfections (on which Dr. Ffrangcon Roberts has many wise things to say). The wary writer can subdue an erratic vocabulary, whatever its complexities and errors of derivation, and still make his message clear; he should not be discouraged by the cries of those who condemn his technicalities, *unless* they can rightly claim that the readers for whom he writes will not know what he means. The summary of an article we recently published was attacked because, among other things, it contained the words " acrocentric chromosome " and " nucleolus organiser ". Groping dispiritedly for an answer, we came upon Manuila's comment: " Le purisme dans le langage médical est le fruit d'un malentendu. Tant qu'il subsistera nous resterons où nous en sommes: dans le chaos."[4]

3. *ibid.* 1958, ii, 215.

4. Manuila, A. *Vie méd.* special number, Christmas, 1960.

Medicine and the Law

Alcohol and the McNaughten Rules

SINCE the introduction into English law of the defence of diminished responsibility, there has been less occasion to invoke the McNaughten rules. Yet these rules are still of importance. The defence of diminished responsibility applies only to murder, whereas the McNaughten rules can be invoked in any criminal case and also, as during the past few weeks, in adultery.[1] There are also some cases of homicide in which the McNaughten rules will be more appropriate as a defence than diminished responsibility. And there are still some British territories in which the defence of diminished responsibility is not available even in cases of murder.

One of these territories is Northern Ireland, and a recent appeal to the House of Lords raises some important issues in relation to the McNaughten rules.[2]

The facts were that one Patrick Gallagher had been charged with the murder of his wife. There was no doubt that he had killed her, but he pleaded at his trial that he was insane or, alternatively, so drunk as to be incapable of having any intention either of killing her or of doing her grievous bodily harm. It was proved that he had a grievance against his wife: she had obtained a maintenance order against him and had been instrumental in getting him detained in a mental hospital. He had made up his mind to kill her and had bought a knife for the purpose and a bottle of whisky either to give himself Dutch courage to do the deed or to drown his conscience after it. He did in fact kill his wife and drank much of the whisky either before or after. There was some evidence that he was an aggressive psychopath, that he had a disease of the mind that was quiescent for considerable periods but which manifested itself from time to time in explosive outbursts.

The jury had convicted him of murder. On appeal, the defence criticised the summing up on the ground that the trial judge had directed the jury to apply the McNaughten test not to the time when the accused killed his wife but to the morning of that day when he opened the bottle of whisky. This was at variance with the specific terms of the McNaughten rules, and the Court of Criminal Appeal in Northern Ireland quashed the conviction of murder. The court certified that the following point of law was involved: " Whether a person in a psychopathic condition which is quiescent may become insane within the meaning of the rules in McNaughten's case as a result of the voluntary consumption by him of intoxicating liquor if the effect of that intoxicating liquor is to bring about an explosive outburst in the course of a mental disease although that disease was not itself caused by intoxicating liquor ".

Giving the leading judgment in the House of Lords, Lord Tucker said that a man might produce in himself a disease of the mind by excessive consumption of alcohol—for example, delirium tremens—and in such a case the question would arise as to whether the disease so produced had resulted in insanity within the McNaughten rules. But this was not such a case; it was not suggested that Gallagher had become an aggressive psychopath as a result of consuming alcohol.

There was some difference of opinion as to whether the accused was in fact an aggressive psychopath. One medical witness said he was, some of the others were prepared to accept that he might be. The real conflict of medical opinion was whether the explosive outbursts in the case of an aggressive psychopath merely diminished or destroyed the power of self-control or whether they prevented him having any knowledge of the nature and quality of his act or that it was wrong.

Continuing, Lord Tucker said that the trial judge was at variance with the McNaughten rules in so far as he had directed the jury to the time when the accused had opened the bottle of whisky. But this must be taken in the context of a careful summing up in which the trial judge had time and again referred to the questions whether the accused knew what he was doing and that it was wrong and had related these questions to the time of killing. What the jury were being told was that they should consider whether the particular disease from which the accused was said to be suffering was of the nature described by the defence—namely, one in which violent outbursts would produce absence of knowledge of the nature and quality of the act or of its wrongness—or whether, as stated by the prosecution, it was merely lack of self-control. In view of the overwhelming nature of the evidence, consisting largely of the accused's own statements, there was no miscarriage of justice.

1. See *Lancet*, 1961, i, 1399.
2. *Times*, July 21, 1961. *Guardian*, July 21, 1961.

The House of Lords accordingly overruled the decision of the Court of Criminal Appeal in Northern Ireland, and the conviction of murder was restored.

The decision of the House of Lords appears to have been based on their view of the facts of this particular case rather than a positive ruling on the point of law put by the Northern Ireland appeal court.

Obsessional Neurosis as Cruelty

A husband petitioned for divorce on the ground of the wife's cruelty. The wife did not defend the suit.

The parties were married in 1952, the husband being then 28 and the wife 27. There were no children. Before the marriage the husband had observed that the wife was more concerned than the average person about cleanliness. During the first six months of the marriage, sexual intercourse took place three or four times; but it then ceased, the wife being disinclined for intercourse. In 1955, the wife's preoccupation with cleanliness and hygiene markedly increased. She would only allow prepacked food to be used, so that the diet became restricted. The preparation of meals was interrupted by frequent disinfection and repeated washing. So much ritual surrounded the household tasks performed by the wife that the husband found it much quicker and easier to do the housework himself. The wife took so long to get ready for bed at night that the husband was seriously deprived of sleep. In 1956, the wife had two periods of inpatient treatment at a hospital, the first time for 3 months and the second time for 4 months. When she left hospital she was advised to continue treatment as an outpatient but she did not do so. Medical evidence was given that the wife suffered from an obsessional neurosis, that she knew the nature and quality of her acts, and that she knew the difference between right and wrong. There was also medical evidence that the husband suffered from strain.

Counsel appearing for the Queen's Proctor as *amicus curiæ* put forward the following propositions: (1) that the state of the wife's health was a relevant consideration on the question whether her behaviour constituted legal cruelty; (2) that a spouse could not be held guilty of cruelty on the basis of acts committed while that spouse was insane within the McNaughten rules; (3) that there was no halfway house between sanity and insanity, analogous to the condition of diminished responsibility in homicide cases in the criminal law; (4) that no impulse could be regarded as irresistible unless the person concerned was insane within the McNaughten rules; (5) that the presence of an express intention to injure was not an essential ingredient in legal cruelty; and (6) that the presumption that a person intended the natural consequences of his acts was applicable, but it was a rebuttable presumption.

Judge LESLIE said that he accepted the propositions put forward on behalf of the Queen's Proctor as correct statements of law. Applying those propositions to the present case, although the wife's conduct was due to illness, it was not due to insanity within the McNaughten rules. The wife must have known that her conduct would have a deleterious effect upon her husband's health. Although her acts were not intended to harm the husband, they were intentional acts which were likely to harm him, and did in fact do so. She had not rebutted the presumption that she intended the natural consequences of her acts. In the result, her conduct amounted in law to cruelty, and the husband was entitled to a decree nisi.

Alway *v.* Alway, *Probate, Divorce and Admiralty Division: Judge* Leslie. July 31, 1961. Counsel and solicitors: Mrs. Margaret Puxon (Woodroffes); A. B. Hollis (Blacket Gill & Small); N. H. Curtis-Raleigh (Queen's Proctor).

D. R. ELLISON
Barrister-at-law.

Special Articles

THE PHARMACEUTICAL PERSUADERS

The Industry, The Doctor, and the Clinical Trial

FROM A CORRESPONDENT*

RATIONAL and specific therapeutics may be said to have begun with the chemical discoveries of Emil Fischer and Paul Ehrlich in the last quarter of the 19th century. Their spectacular development is attributable rather to the organic chemists and the pharmacologists than to the clinician, who has had comparatively little to do with either stimulating or developing rational therapeutics. Although there has been an increasing need for clinicians to test laboratory products on their patients, clinical medicine is still in the era of rational diagnosis—exemplified by such names as Virchow, Aschoff, and Osler, and has not begun to apply the same rational approach to the trial of new substances.

The era of therapeutics, as we know it today, coincides with a time of explosive industrial development and the small laboratory has been replaced by complex organisations which are part of the economic apparatus created to exploit and advance natural and human resources.

In this period of competitive coexistence, 20th-century man is being exposed to many persuasions. Throughout our lives we are being overwhelmed by what Packard has called " the hidden persuaders ". It is true that in the past twenty years some original discoveries, and certainly most of the developments of new drugs, have stemmed from pharmaceutical organisations that produce new substances for therapy; but these same organisations also spend a large amount of their funds and time on persuading the customer that their product is better than their competitors' and fills a need. It would be naive to believe that the pharmaceutical industry exists in order to advance science, cure disease, or promote humanitarian good will: these are only incidental by-products of their very clear and natural aim to make profits and sell their wares.

Once this is fully understood by the customer—i.e., the medical profession—everything that needs to be said becomes a little clearer. A drug house is defined as " ethical " if it does not advertise certain products to the patient while advertising them to the physician, and it may or may not have other characteristics usually associated with the word " ethics ".

METHODS OF PERSUASION

It might be comforting to imagine that the medical profession on the whole are more clear-thinking and resistant to sales pressures than the rest of the population; but the evidence provided by the drug companies themselves seems to counter such a supposition.

What are the means by which the industry is persuading us doctors that we need their drugs, that these are good for our patients, and that we should continue to use them? They may be divided into plain advertising, unsubtle advertising, and subtle advertising. When a new drug is sent out to be tried by a number of clinicians, the drug house is motivated by a desire (1) to know whether or not the substance works, and (2) to find out whether it is acceptable both to the doctor and the patient, but also (3) to tell as many doctors as possible, even at that early

* This paper is written by a teaching member of an American medical school. He prefers to remain anonymous lest any of his remarks should embarrass his colleagues.

stage, that this drug is being tried and may in due course be sold commercially.

INVITATION TO UNDERTAKE TESTS

What are the gambits employed on this initial approach by the drug company? First of all, you must be persuaded that the compound which is sent to you for testing is worth testing. Naturally, if you are in cancer research and they are offering you a new antimitotic agent, the mere mention of this would arouse your interest. However, as more often they are likely to come to you with a new aspirin or codeine-like analgesic, or a " new " steroid, or a new vitamin for cold sores, something definite may be needed to get you interested. Several ploys have been used in this. A common one is to tell you at an early stage that you have been particularly selected in views of your qualifications, facilities, interest, brilliance, or (perhaps more important, and they do not usually say this) need for advancement, to test their new substance. If you harbour a lingering doubt, you may be told that the well-known university doctors at X, Y, and Z have just received the substance also and have very recently begun testing it—implying that you really should count yourself lucky to be mentioned in one breath with these important people.

The reputable drug company will then issue you a brochure telling you something of the chemistry and pharmacology of the new compound, and of the dose they recommend that you use on your patients. As may be imagined, these brochures differ very much in quantity of material presented, and (more importantly) in quality. It cannot be emphasised too strongly that you, as the prospective investigator, should read this brochure in great detail, and most particularly those sections dealing with the safety testing or toxicity tests which have been performed before you get the substance.

There has been a tendency of late for drug houses of all sizes and reputations to become somewhat careless with these toxicity tests, and examples are known where the onus of subacute and chronic toxicity has been put in human testing, where it certainly does not belong. The reasons for this let-up in safety precautions is partially the flood of new synthetic chemicals, released by the chemists, which have some activity in the pharmacological laboratory; but it is also due to the willingness of many clinicians (provided their interest is sufficiently aroused) to try first and be sorry after.

Quite obviously, requirements for toxicity testing vary, depending on the use to which a drug is to be put, and the standards for a drug to treat cancer differ from the standards of a drug to treat the common headache.

Toxicity tests include the acute, subacute, and chronic. Acute toxicity tests are designed not only to provide us with the L.D. 50—i.e., the dose which kills 50% of the animals—but also shows us how they die and what they died of. Subacute and chronic tests are designed to show up any clinical or biochemical effects on organ function. At intervals animals will be killed and histological section will try to unravel any deleterious actions on selected tissues, such as heart, liver, kidneys, pituitary, thyroid, optic nerve, adrenal, and gut. Sufficient numbers of several animal species should be involved, but certainly one species should be a mammal, such as a dog or monkey. For initial testing, no drug should be given to a patient for a period longer than it has been given to a mammal, without effect on biochemical and histological findings; these are minimum requirements and most workers will insist on a period in animals twice as long as that for which it is intended to give the drug to a patient. Further than all this, it may be said that no new drug should be given to man unless a mammal has had it for at least four weeks, and the previous remarks should be applied to intended further chronic human experimentation.

When asked to test a new substance not many of us may have had the pharmacological training and experience necessary to judge the safety of pharmacological testing procedures, and in these circumstances one should be strongly advised to seek competent advice and support from pharmacologists within an independent hospital or university environment. Where there is the least doubt, one should adamantly refuse to use the new substance even though this may result in the rejoinder that Dr. X, Y, and Z have already tried it for ten days and that no ill effects have resulted so far. If these points were better known and appreciated, drug companies would find fewer doctors X, Y, and Z, and the pressures might somewhat ease. During the past five years there have been several examples of premature, faulty, injurious, and fatal drug trials.

Who should feel competent to try new substances? This question is tied up with the concept that possession of a medical degree promotes us to a status of scientific excellence and ability of judgment. This, of course, is a most fallacious assumption. Opinions, prejudices, and views are only too easy to come by, but objective, rational experimentation with a new compound demands, in order of importance, time, facilities, special training, and more time. As pointed out, time—to think, to plan, and to execute the human experiment—is more important than any other factors; and, if you find these cannot be provided, it would be better not to engage in the trial of a new substance.

THE TRIAL AND THE REPORT

Let us assume that you have agreed to try a new substance and it will be provided to you free by the drug firm. In addition, they may support your department by paying for a technician, and they may indeed offer to support you personally, either by direct grant, by taking you out to dinner, or by paying for you to attend a distant congress. There is no harm in all this as long as you feel you are not beginning to eat out of their hands and get tied to them in any way. It is, of course, difficult to define the exact point when this tie-up may begin to influence your judgment, and in ideal circumstances, which do not exist at present, complete independence and lack of support from the firm which supplies a drug might be insisted on. The offer of support may take less subtle forms of offering to take your figures and have the firm's statistician work them through, and even to write your paper for you. This is done not infrequently, and the spread of this practice would in time seriously jeopardise the sort of objectivity which one hopes is, in the final outcome, the main aim of all concerned.

If you find your set-up, your fellows, and your technicians almost entirely supported by one or other drug firm, you may quickly find yourself in the position of a testing factory, with all the disadvantages inherent in being tied to an organisation that must produce results eventually, in order to survive.

Many congresses and symposia, indeed whole academies of science, are now being sponsored by the pharmaceutical industry; and whenever you (usually on their expense accounts) proceed to read a paper on one of their drugs at

their meetings, you may find that your publication is spread in tens of thousands of copies throughout the country to promote the sales of the compound you are discussing. Clearly this is an unsatisfactory state of affairs, unless you are superhuman enough to withstand the pressures.

The systematic and critical group reading of medical journals should be common practice in our medical schools. In this way we would notice that an inordinate proportion of papers in many journals give positive reports on new drugs and advocate their widespread use. Even if the article itself, or the figures, are something less than complimentary to the new drugs, the summary will quite often contribute a ray of hope and end by saying that "further trials of this interesting new substance are warranted". In fact, one cannot help wondering whether the conclusions of some papers are written by the same author as the substance.

Statistics and certain concepts, such as double-blind trials, are on everyone's mind today, and the misuse of these features often helps to persuade the uninitiated (and let us admit that most of us are really uninitiated) to accept things at their face value.

Taking facts out of context and misapplying them to support an argument is one of the oldest weapons of demagogy, and pharmaceutical advertising makes full use of this.

NON-SUBTLE ADVERTISING

Some forms of advertisement are promoted by a devoted band of people variously described as drug salesmen, research associates, and the like. These people, as in all professions, vary in calibre and training, and some of them are intelligent and understanding. However, the nature of their calling should make it very obvious that we cannot expect from them an impartial and unprejudiced statement of fact. Far from it. Many of them are highly trained personality experts with experience in methods of approach, contact, and persuasion. Their stamping-ground is usually well prepared by supporting the semi-indigent members of the medical profession (and who of us doesn't consider himself semi-indigent?) with free drugs ad lib. for our own use and that of our family.

Perhaps more important, the invasion of our independence already begins in a planned fashion during medical student days. With what seems to be the tacit approval of the authorities, pharmaceutical firms are giving planned gifts each year to medical students, to condition them to the kindness, beneficence, and general acceptability of the pharmaceutical firms in question. This planned conditioning organised like psychological warfare can be seen on a wall chart in the teaching room of one of the large drug houses. It must be clear, even to the simplest, that there is method in this munificence, and that somebody eventually has to pay for all their good works.

There is ample reason to be disturbed by the very considerable take-over of postgraduate medical education by the pharmaceutical industry. Ought we to allow forces which, by their very inception, must be partial, prejudiced, and pragmatic to take over an area of learning which ought to be independent and objective?

Plain advertising, in the medical journals, can be complex and appeal in numerous ways. In some journals, there is some slight limitation on what may or may not be said in advertisements, though most medical journals seem to separate sharply the functions of the editorial committee and that of the advertising and publicity staff. Often, too, a pharmaceutical company will issue its own house journal, which is distributed well and in whose columns it may with impunity attack, deride, dissuade, and perform any number of miracles of modern advertising. Somewhere in between the so-called independent medical journal and the pharmaceutical house journal are medical journals which are being paid for almost entirely by one or other pharmaceutical house. There can be little doubt that, through the enormous pressure of advertising revenue, the industry, to a greater or lesser extent, also controls many of the journals assumed to be independent.

Many, if not most, medical congresses are now organised and supported by the pharmaceutical industry, and it is common usage that papers have to be submitted to the pharmaceutical company before the meeting which the company is sponsoring. This obviously provides the required slant and tenor of the meeting that is being organised.

Even the free supply of drugs for non-paying patients is used by industry as a not so subtle weapon to obtain manuscripts before publication. In a recent case, continuation of drugs for patients who had become dependent on a new substance was made dependent upon an author's passing across a manuscript (not yet accepted by a journal) to a pharmaceutical company.

In the United States some of our indigent clinics have to rely upon gifts from pharmaceutical companies to allow proper treatment of patients, and in this way unsatisfactory drug mixtures in combination may be put to clinical testing which would not normally be approved for either routine therapy or planned experiment.

It should not be thought that the trends and developments commented upon in this paper are either limited to, or indeed most widespread in, the Western hemisphere. These are world-wide phenomena and of concern to the practice of medicine everywhere.

CONCLUSION

Exciting new developments have come from initiative and research activity of the pharmaceutical industry, and it behoves us to work with them. But we must recognise their inherent weaknesses, resist persuasion against our better judgment and knowledge, and jointly attempt to influence them to use the facilities to the end which we, as physicians, are mainly interested in—to wit, the rational treatment of disease.

RECOMMENDATIONS FOR THE NOMENCLATURE OF HÆMOGLOBINS *

Chain Nomenclature

There is now general agreement on the naming of the peptide chains of the major components of normal human adult and fœtal hæmoglobins as the α, β, and γ chains: for instance, adult hæmoglobin is written as $\alpha_2^A\beta_2^A$ and fœtal hæmoglobin as $\alpha_2^A\gamma_2^F$. The superscripts A and F refer to the fact that the particular chain is the one found in the human adult and fœtal hæmoglobins. It is recommended that this practice be continued and that the symbols α, β, and γ, without superscripts, be reserved for those occasions when reference is being made to, for example, chains in general.

Information concerning the structure of the chains of hæmoglobin A_2 is now sufficient to indicate that one of the chains is identical with the α^A chain, while the second differs in a number of residues from the three foregoing chains. In addition there is evidence [1] to indicate that the genetic control of this unique chain is independent of the genes for the α, β,

* These recommendations are appearing also in the *Journal of Biological Chemistry*, August, 1961.

1. See, for example, contribution by R. Cepellinini to the Ciba Foundation Symposium on Biochemistry and Genetics, 1959.

and γ chains. It is therefore recommended that this chain be designated as δ^{A_2}; Hb A_2 is then written as $\alpha_2{}^A\delta_2{}^{A_2}$. Again, one could refer simply to δ chains in the general case.

The simplest method of naming the tryptic peptides of a chain is to number them in the order in which they occur in the chain, beginning with the N-terminus. The symbol for the chain is included as a part of the designation. The letters Tp are included to identify that these are the peptides obtainable by tryptic digestion. For example, the third tryptic peptide of the α chain would be αTpIII in this system. Where a lysyl bond is not attacked under the conditions used, the symbol for the resultant "dipeptide" or "double peptide" would contain the numbers appropriate to both tryptic peptides—e.g., αTpI,II. From the published structure of the α and β chains [2] and from the aminoacid composition, it is evident that the α chain will contain the tryptic peptides αTpI to αTpXIV and the β chain the tryptic peptides βTpI to βTpXV. It so happens that the tryptic "peptides" αTpVIII and βTpVIII are lysine. In addition, the present methods of tryptic cleavage do not break the bond separating the expected tryptic peptides αTpXII and αTpXIII, nor the bond between the expected peptides βTpX and βTpXI. In view of the possibility that these bonds might be split in some experiments at a later date, it is felt that the numbering system should correspond with the theoretical number of tryptic peptides.

When the complete sequence of the chains is determined beyond question and is published, then a more specific designation involving residue numbers should be adopted. Thus, βTpI can be designated as βTpI-8.

Nomenclature of the Abnormal Hæmoglobins

An ideal nomenclature system for the abnormal hæmoglobins would provide for adequate designation of the chemical structure at each stage of the investigation. The following system is an attempt to meet this requirement.

When only the chain in which the abnormality resides is known, then the hæmoglobin may be written as $\alpha_2{}^A\beta_2{}^S$, or $\alpha_2{}^A\beta_2{}^{D\,Punjab}$. When the abnormality has been located in a particular tryptic peptide, as by fingerprinting, then the designation should be, for example, $\alpha_2{}^A\beta_2{}^{TpI}$. When the aminoacid composition of the tryptic peptide indicates a particular aminoacid substitution, then this will be indicated as $\alpha_2{}^A\beta_2{}^{TpI(Glu\rightarrow Val)}$ for Hb S. Finally, when the aminoacid interchange has been located at a particular residue position in the chain, the fully descriptive formula, as in the case of Hb S, would be in the form: $\alpha_2{}^A\beta_2{}^{6Val}$.

Presumably, for use in formulæ describing experiments such as reassociation, it will be necessary to define in a given paper a one-letter designation for a particular hæmoglobin. For example, the formula $\alpha_2{}^I\beta_2{}^S$ could be used, provided that wherever possible the individual hæmoglobins have been defined, as, for example, Hb I as $\alpha_2{}^{16Asp}\ \beta_2{}^A$ and Hb S as $\alpha_2{}^A\ \beta_2{}^{6Val}$.

It is strongly urged that no further letters be assigned to abnormal hæmoglobins. Newly discovered hæmoglobins, prior to their chemical identification, should be known by the letter designation of the previously described hæmoglobin whose electrophoretic mobility they most nearly resemble. To the letter should be attached a subscript indicating the geographic origin of the new hæmoglobin.

The above proposals originated during a Hemoglobin Structure Workshop held in Boston, Dec. 14–16, 1960.

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V. M. INGRAM
Professor of Biochemistry.

2. Braunitzer, G., et al. *Z. physiol. Chem.* 1960, **320**, 283, 1960, **322**, 96; Hill, R., Konigsberg, W. *J. biol. Chem.* 1961, **236**, PC 7.

The Wider World

BOLIVIA

A. JOHN ROBERTSON
M.D. Lpool, M.R.C.P.
CONSULTANT PHYSICIAN, LIVERPOOL ROYAL INFIRMARY

AT the end of the last century the President of Bolivia felt he had been insulted by the British Minister in La Paz. For this, the Englishman was run out of the city, stripped naked on a donkey. When the incident was reported to Queen Victoria, she ordered a gunboat to the vicinity to deal with those who had dared to so ill-treat her Representative. It was explained to her that La Paz was out of range of any vessel unadept at mountaineering: she therefore had Bolivia deleted from all British maps. By this geographical ostracism Bolivia has become a country unknown to most British people, who may be unaware that it is a South American Republic without a coast-line.

This fable, retold by Osborne [1] in his excellent book, is as good an excuse as any for our lack of knowledge of the country, internationally important for many years for its mineral wealth, and now a danger spot because of its economic difficulties. Throughout this article superlatives will be used in an attempt to portray a land of violent colour and contrasts and geography, and if phrases such as ". . . in the world" recur frequently that is simply because they are true.

GEOGRAPHY

South America has its backbone in the Andes, a tremendous range with many peaks of over 20,000 ft., which stretches fairly close to the western seaboard for about 5000 miles from Colombia in the north to the Straits of Magellan in the south. On the south-eastern border of Peru the Andes splits into two gigantic granite ridges about 150 miles apart, and these travel roughly south-east for about 600 miles, enclosing a vast high plateau (the Altiplano) of 13,000 ft. altitude (fig. 1). The western ridge borders Peru and Chile, and on the Altiplano and the eastern ridge live the bulk of Bolivia's sparse population. This Royal Eastern ridge—Cordillera Real—is the site of most of Bolivia's minerals, and it soon slopes off eastward to the "Green Hell" of Julian Duguid and the jungle and swamps and tributaries of the Amazon—which form over two-thirds of the country.

On the Altiplano there are hundreds of miles of flat dirt roads, now maintained by the United States Point 4 Mission: the surface varies with the weather, and has to be scraped frequently in the short rainy season. The traveller has warm sun with magnificent deep blue-black skies by day, and freezing air with no trees or shelter or warmth or light by night.

Fig. 1.

To get out of the Altiplano it is generally necessary to cross over a mountain pass with the crest (La Cumbre) at about 15,000 ft. This makes

1. Osborne, H. Bolivia. 2nd ed. London: Royal Institute of International Affairs, 1955.

Fig. 2—Road near La Paz.

the Pass of the Condor (15,700 ft.) on the railway to Potosi *one* of the highest passenger lines in the world. As can be imagined, communications are a very difficult problem for the country, which is about the size of France plus Spain (or Texas plus California), and has only a few hundred miles of good paved road. " The roads are uniformly bad, usually incredibly bad, and often most dangerous ".[1] Even main roads near La Paz are liable to be swept away by rain and landslides (fig. 2). There are no fences or walls to the precipitous edges of roads cut in the mountain side, though the many R.I.P. crosses that mark too much enthusiasm save the road department the expense of danger signs.

PEOPLE

There was a well-developed Inca civilisation, and their terracing of land on the steeply sloping mountains can still be seen easily, especially near Lake Titicaca (fig. 3), the highest navigable lake in the world at 12,500 ft. The Incas probably had their capital near Tiahuanaco, where a few monoliths from pre-Inca pre-Christian times that have escaped souvenir-hunters may still be found (fig. 4). In the early 16th century this part of South America was invaded by the Spanish, who exported all the silver and gold they could find, destroyed the Inca culture with ruthless efficiency, and were thrown out just less than three hundred years later. It is probable that the cruelty, greed, and persecution during this exploitation were exceeded only by the corruption and injustice that followed the expulson of the Spanish.

Fig. 3—Balsa boats on Lake Titicaca.

In 1825 the State of Bolivia was founded by Simon Bolivar and the Venezuelan general Antonio José de Sucre. At that time it had about 900,000 square miles, but its natural resources have cost it much territory. In the late 19th century it lost about 200,000 square miles after disputes with Brazil over rubber; when nitrates were found its coastline was taken over by Chile; when oil was suspected in the south-east, the horrible Chaco war gave almost 100,000 square miles to Paraguay; and it now has less than half its original land.

Only about 10% of the population are literate, though since the last major revolution in 1952 there has been a slight increase in education—almost all for the children of miners. Roughly 5–10% are of fairly pure Spanish descent (" white "), about 30% have varying proportions of Indian blood (" cholos "), and about 50–60% are Indian. The Quechua and Aymara Indians (fig. 5) have an average income which has fallen to an estimated 60 dollars U.S. per year, and until recently very few had votes. In 1951 only 200,000 out of a population of $3^1/_2$ million Bolivians were on the electoral role, and only about 100,000 actually voted. No doubt the electorate thought that too wide a franchise would hasten the inevitable coming of the world's first Indian State. The Indians are said to be conservative, ignorant, and unambitious, and to be addicted to alcohol and coca; but this opinion may be in part an inheritance from Spanish Colonial days, when Indians were expendable items. However, the present Government has given many Indians a vote.

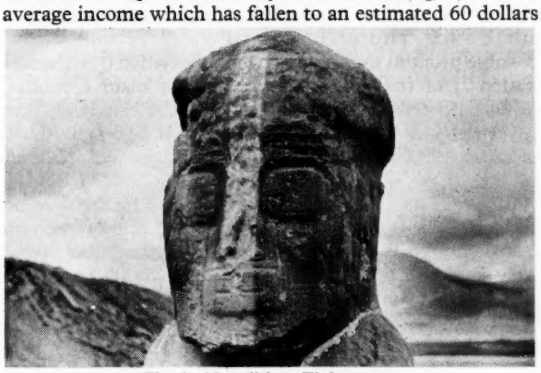


Fig. 4—Monolith at Tiahuanaco.

MINERALS

Even before the Incas, copper was mined, and gold and silver used for decoration. About three hundred and fifty years ago the hill-tops could be seen twinkling at night with the thousand lights of tiny charcoal furnaces, pierced with holes to let the wind blow through, to smelt copper and silver. In Spanish times silver was the most important mineral, and the Bolivian flag shows Potosi mountain on it. In the early 17th century Potosi was probably the richest and most expensive city in the world, but now it can merely claim to be the highest city in the world at 13,250 ft.—well over 1,000 ft. higher than Lhasa in Tibet. From Potosi mountain—seen in fig. 6 from the roof-top of the one-time Spanish mint—the Spanish took so much silver that it was possible to have a silver coinage

in Europe. "Enough to build a bridge from here to Spain," said our host, but added wryly that no doubt the Elizabethan privateers had had their share.

Fig. 5—Indians in Southern Bolivia.

During this century tin has been a source of great wealth, though this natural resource has not been exploited mainly for the welfare of the people. In the Revolution of 1952, it was politically convenient to try to keep more of the possible profit in the country by expropriation ("nationalisation") of the mines. In reality the main economic result has been to change the value of the boliviano from B 190 per U.S. dollar in May, 1953, to B 12,000 per U.S. dollar in 1960, and to make ordinary labour discipline in the mines virtually non-existent.

All important deposits have been found by accident by Indian peasants or Spanish priests, and not by modern instruments. Tin occurs in the most inaccessible spots: who would suspect it, for example, at 17,000 ft. on the 19,000 ft. Chorolque mountain in southern Bolivia? (fig. 7). Mining is done by drillers (who probably have the highest silicosis-rate in the world) from horizontal shafts dug into the steep mountain sides. The ore is then transported to a plant for concentrating, bagged, and shipped to England—because of the great technical difficulties (in fuel, transport, manpower and economy) of smelting it on the spot. It is this export of tin-ore concentrate (done now by the Corporacion Minera de Bolivia-Comibol) which brings in about 80% of Bolivia's foreign currency, though there is so much labour difficulty (putting it politely) that it is said to be produced at a loss.

MEDICAL CARE

The Altiplano Indian has no medical care, though witch-doctors are available. I was assured (by "whites") that the Indians did not expect it and would resent it. Those who work in the mines (a nominal 20,000) and their families are cared for by Comibol doctors, and each mine has its hospital.

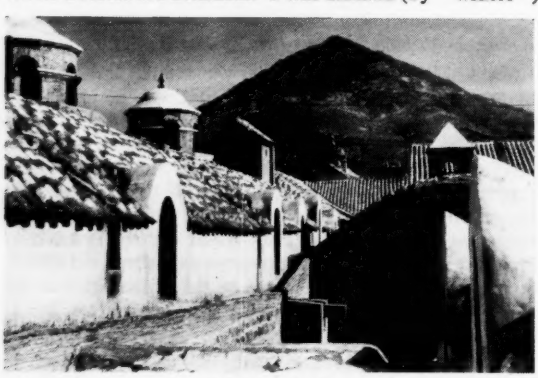


Fig. 6—Potosi.

It is estimated (perhaps unkindly) that the Bolivian medical student cannot get more than a total of two and a half years' training if allowance is made for holidays due to saints' days and anniversaries of revolutions. There are about 850 registered doctors, though some of these are specialists. About 400 are employed by the Caja Nacional de Seguridad Social (C.N.S.S.): since the C.N.S.S. appears to be "broke", many are not paid, some are on strike, and the service as a whole is in need of complete reorganisation. About 100 are employed by Comibol, a small number by the nationalised petroleum industry, and the rest are in private practice. There is an extremely ambitious social programme which requires the employer to pay a contribution of 30% of the employee's wages, but the country is not yet sufficiently educated to use it.

There are no *reliable* statistics about anything, but on the Altiplano the survival-rate of children in the first year of life is said to be 50%. By very hard work in one small community near Cochabamba, a pædiatrician and an American-trained "district" nurse have reduced the infant mortality from 40% to 10% for babies under one year old.

Industrial medicine has very little part, if any, in the medical student's curriculum, and a comment from many Comibol doctors was that they were there to treat patients, and not to go into the mines or do any preventive medicine. There is a wonderful opportunity to find out exactly which occupations within the mines and plants have a health hazard, both from accidents and from pneumoconiosis, inasmuch as safety precautions are conspicuous by their absence. Although there are many "photographers", there are only about four properly trained radiologists in the country. What is worse, the accuracy of diagnosis is seldom checked, because there are no pathologists as understood in Europe and North America, since virtually no necropsies are made. Curiously enough, the clinical pathologists, who do blood-counts and other blood analyses or urine tests, are well trained, are not medically qualified, all have to be Government-registered, and seemed to have a high standard in the relatively limited field in which they work. They are a few specialists, trained in the Argentine or Chile or Mexico or the United States, whose work is obviously of high calibre.

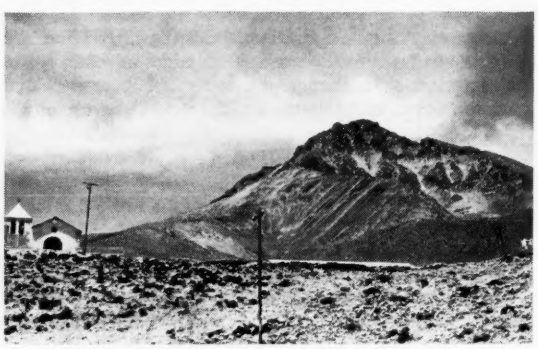


Fig. 7—Chorolque (19,000 ft.), southern Bolivia.

THE ALTITUDE

Altitude is discussed rather like the weather in England, but only with foreigners. Most visitors to Bolivia fly in

from sea-level at Lima, Peru, to the highest commercial airport in the world at 13,400 ft., just above La Paz city, the highest seat of Government in the world at 12,700 ft. Friends in Lima warn the traveller of the terrible place he is to visit—and offer to drown his sorrows. During the fascinating trip over Peruvian desert with the snow-peaked Andes clearly visible 100 miles away, the plane dodges the mountains by squeezing at 18,000 ft. through the passes on to the Altiplano, and again the buffeted passenger is encouraged to solace himself with cheap liquor. When he steps out of the plane at La Paz, having ascended 13,000 ft. in a few hours, he is inevitably breathless—and next day the headache is put down to the altitude and not the whisky. There are undoubted physiological changes,[2] but, though of course every visitor will be breathless with exertion, there is no reason to suppose that after a few days any other symptom is associated with these changes. Almost all my trip was spent between 12,000 and 17,000 ft.: after acclimatising for one week, to climb vertically 65 feet up a pitch black "chimney", 3 ft. × 3 ft., at an altitude of 14,000 ft. and about a mile inside the mountain (fig. 8) was unpleasant, particularly with too much clothing for a temperature of 90° F. But a later experience at Chacaltaya (fig. 9), the highest ski-lift in the world at about 17,200 ft., brought no symptoms except dyspnœa. It is said that sleep is difficult: a combination of 'Coca-cola' and Bolivian coffee (surely the nicest in the world) can guarantee a sleepless night unless taken in moderation.

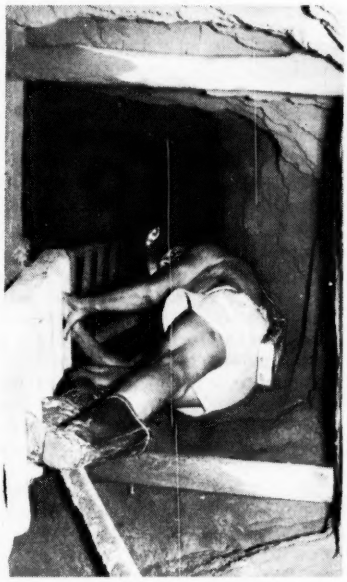


Fig. 8—"Chimney" in Colquiri tin mine.

Fig. 9—Ski-lift at Chacaltaya, during snow shower.

2. Hurdato, A. *Ann. intern. Med.* 1960, **53**, 247.

VISITORS

A visitor to this wonderful country of the three R's—Rumba, Romance, and Revolution—cannot hope to get more than a superficial impression in four and a half weeks (particularly with travel limited to the Altiplano and Cordillera Real), though contrasts are obvious enough. In La Paz there are steaks of better quality than in any first-class British hotel, cooked perfectly, and accompanied by music from *My Fair Lady*. But there is a wait of twenty-five minutes for the soup, and the hotel will have twice the number of staff it needs, who cannot be dismissed without seven months' wages in compensation. Outside shacks in country villages there are bits of pig to be bought, cooked black over charcoal fires: a lady was accused recently by the police of selling roast pig in the street under false pretences, since the meat was her husband suitably dismembered. There is the drive over desolation at La Cumbre (15,000 ft.) (fig. 10) along an unforgettable road, to the tropical heat and bananas in Las Yungas (3,000 ft.), only 30 miles from La Paz as the eagle flies, but 70 by road.

Scenically it is a superb country. Even at the end of the winter the skies are still a magnificent dark blue, with a clear atmosphere that enables Illimani (21,150 ft.), which overlooks La Paz, to be seen clearly from 100 miles away and makes it plain how much vision depends on clean air. A mountain side may be purple and green and orange, with weather erosion that suggests a landscape "created by the unbridled imagination of a lunatic in love with beauty".[1] The 20,000 ft. snow-covered peaks form a vivid background to the very few eucalyptus trees, the Inca terracing, and the flocks of llamas, and it is the colour of the sky which helps to relieve some of the barrenness of this Altiplano. "A beggar sitting in a chair of gold", was once used to describe Bolivia—but it should be added that surely the chair is placed in the heavenly sky.

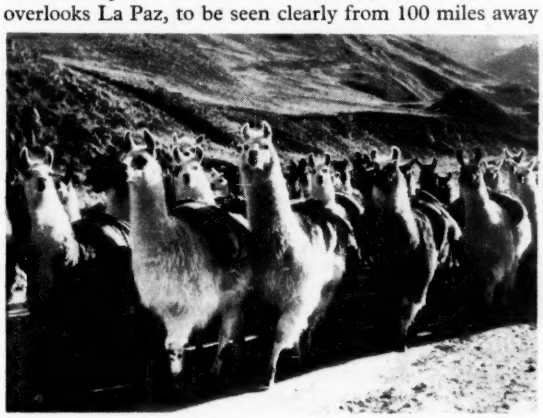


Fig. 10—Llamas near La Cumbre on road to Las Yungas, near La Paz.

In Bolivia I was the guest of Comibol, and am grateful to their president, Dr. Bedregal, for this privilege. It is a pleasure to record that throughout the country I was given a most courteous reception by everyone, from the President of the Republic, His Excellency Dr. Victor Paz Estenssoro, downwards. I am very grateful to the mine managers, engineers, doctors, and many Bolivian friends for their advice, frankness, and unforgettable kindness and hospitality. The staff of the British Embassy at La Paz could not have been more helpful, and made me proud to be British.

This unusual trip was made possible by Consolidated Tin Smelters, through the generosity of their managing director, Mr. Clifford Waite. The company are not responsible for any views I expressed either in Bolivia or in this article.

In England Now

A Running Commentary by Peripatetic Correspondents

IN the U.S.S.R. motor accidents are rare—not so much because of the standard of driving as because there are not many cars on the roads to get entangled with each other. Accidents involving foreigners are more unusual still; but any British tourist who is unfortunate enough to be the victim of such a mishap can be assured of V.I.P. treatment. He will, indeed, receive all the benefits of the Soviet health service, including a feature on which our N.H.S. would be unable to reciprocate—namely, a full-time, day-and-night, Intourist interpreter.

One of the striking features of a Russian hospital, as I saw it, was the absence of bustle and urgency. There is a plethora of doctors and a dearth of nurses, but nobody ever seems to hurry and there is plenty of time to chat. Axillary temperatures are taken more or less regularly, and meals are served within an hour of the scheduled time; but bedmaking, washing, and all the rest of the English hospital routine seem to go by default. The spectre of Matron does not exist—in fact during a 4-week stay she was neither seen nor spoken of. The nurses do a 24-hour shift with nominally 48 hours off; but during the holiday period, which is spread over some 3 months, they are back on duty the next 24 hours. One sister has under her jurisdiction several small wards, with a few nursing auxiliaries and ward-maids to help her. Although she stands on her dignity when it comes to bedpans, she is clearly unaware of the rigid caste system inherent in the British nursing profession. There is no differentiation by uniform, and in fact the whole of the nursing and domestic staff of the hospital wears the same uninteresting and not always very clean white pinafore.

This pinafore, together with a scarf-type cap, is worn by shop assistants, kitchen, and laundry staff, and certain hotel employees, and in the hospital it provides perhaps a clue to the status of the nurse in the social hierarchy. Under a recent law compulsory schooling is to be reduced from ten to eight years for those who wish to enter any of the above, and similar, callings.

Because nursing is not given a high social rating, and because the more intelligent girl who is drawn to medicine will naturally prefer the financial rewards of being a doctor to those of being a nurse, many duties undertaken in this country by the nursing staff are, in Russia, the responsibility of the doctor. It was the doctor, for example, who adjusted the radiant-heat lamp to dry the plaster-of-paris, and the qualified dentist who performed the daily oral hygiene for a fractured jaw.

To me the nurse's life—with little responsibility, long hours, and inadequate and antiquated accommodation—seemed a dreary one; but I did not at any time hear a single grumble. Maybe this was for a foreigner's edification but I doubt it: rather was it part of the indoctrinated docility of the Russian today, which is a depressing and frightening aspect of the Soviet regime. In no Western country with such a high standard of surgery and professional skill would a 500-bed, mainly acute, hospital in a large provincial town be without electric bells—or for that matter any other type of bell—have no other office for Sister than the corridor, and have wards entirely without running water.

Sanitation, or the lack of it, is perhaps the unfairest point of comparison as between Soviet and British hospitals. One can only hope that every British accident case can be brought home before he becomes ambulant. His memories then of a Russian hospital will be of infinite kindness and care, and he will be blissfully oblivious to what goes on outside the four walls of his room or ward.

* * *

I am waging a one-man campaign against the strange term "space-occupying lesion". Except for a mythological one, any lesion must occupy space whether it be a biochemical lesion, physiological lesion, or the more common lesions that we see in orthodox pathology or in everyday clinical work. The notion that there can be a lesion of the brain that does not occupy space has always struck me as one of the incredible foibles of neurologists and one that did them a little credit. If one means an expanding tumour or swollen area, a compressing structure, a rapidly growing metastatic lesion, the meaning can be set down clearly and without throwing the reader into contortions in his effort to conceive of the difference between a "space-occupying lesion" and a "non-space-occupying lesion". Even though this word has a hoary tradition behind it, it is an excoriation on the face of good clean English speech.

* * *

My brother developed a sore throat and a severe cough for which his doctor prescribed a brown medicine. It was foul-tasting, rather nauseating, and did little to relieve his cough. The symptoms persisted for several days and the family pressed me strongly to do something about it. I hesitated to interfere with a colleague's treatment and therefore confined myself to reassuring my brother that he would get better soon. A week had passed without any improvement when Uncle Ben, who makes his living selling woollen goods, paid us a visit. There did not seem to be any conventions governing professional relationships between general practitioners and woollen merchants, for within five minutes of his arrival Uncle Ben was advising my brother to pour the brown stuff down the sink and get himself some 'Gee's Linctus'. He could get it at Boots or any other chemist, and there was no need to bother with the doctors who were pretty useless anyway. The medicine was duly poured down the sink and the linctus procured. Two days later my brother was well. The family now call Uncle Ben whenever any medical problems arise.

* * *

We all like to think that we do our bit to help the family budget; so when it was found that our house, which is classed as a minor ancient monument, needed reroofing, with some alteration of the roof-line, I decided to remove the chimney stacks down to the existing roof-level before the contractor took over. Plugging away manfully, on my off-duty evenings, my first clanger was to drop a bucketful of bricks, just missing the dog. As my wife pointedly remarked, it was not going to be a very cheap job if I started by knocking off the children one by one. And then I dropped my hammer down a chimney. My by now not so dutiful wife listened at each fireplace in turn while I shouted down the one into which I thought the hammer had disappeared. Finally we decided to remove the sealing around the kitchen fireplace, which had long been blocked off, and recently redecorated. No hammer was found. The 18th-century ancient monument, proudly carrying its new roof, now has a 20th-century hammer hidden somewhere in its bowels, ready to gladden the heart of some archæologist of the future.

* * *

Soldiers are supposed to be versatile and use their initiative, but I was taken aback when the C.O. stopped me and said that I was appointed unit veterinary officer as from then, and I was to visit the hospital pig, said to be seriously ill. A conversation in fragmentary German with the farmer elicited that it was off its feed and coughing, and it seems that when pigs cough they have pneumonia. Moreover the farmer knew the treatment indicated: a penicillin injection. Four locals straddled and restrained the animal, and showed me where to pierce the skin—in the neck. My efforts, and the danger of receiving a savage lunge by the animal when it felt the prick and was precariously held back by the farmers, were rewarded by the patient's recovery.

* * *

When I inquired how my patient's operation had gone, the surgeon launched into a description of his own trials and tribulations during the operation. "It started as a hemi-colectomy—in a patient aged 21 years—but my suspicions that it might be a carcinoma of the colon were confirmed when a congenital colonic polyposis was found, with obvious malignancy of some of the polyps. The total colectomy took four hours. It half killed me." He seemed quite puzzled when I asked, "And how did the patient get on?"

Letters to the Editor

LONG-TERM ANTICOAGULANT THERAPY

SIR,—In your leading article of July 15 you did me the honour of suggesting that your earlier policy suggestion had been influenced by a condensed review of existing evidence by myself and Parry.[1] In view of the " wind of change " I have studied the new evidence of Thomes et al.[2] on which you seem to have changed your mind.

Although their trial has many statistical defects—such as small numbers observed beyond the fourth year, transfer of patients from the treated to the control series so that observation on the latter begins at a later date, and unclear reasons for transfer—the patients appear to be well matched in respect of age and previous history. The method of counting " recurrences " is of course open to substantial subjective error and possible bias, as will emerge below. From the figures on survival, 73% of the continuously treated and 67% of the cases discontinuing treatment lived five years. This fits with the general life-expectancy of such patients as suggested in our own paper. In order to demonstrate advantages from treatment, however, Thomes et al. then eliminated patients with enlarged hearts, cardiac decompensation, and diabetes. 31 patients were thus excluded from the treated group, with a remarkable improvement from 73 to 91% five-year life-expectancy. The elimination, on the same grounds, of 18 cases from the smaller untreated group only improved their five-year expectancy from 67 to 72%. The " treated " figures have thus been adjusted by removal of a large number of dead patients, while hardly any such embarrassments have been removed from the " untreated " series. As both groups seem to have started off with the same proportion of cases with cardiac enlargement or failure, it would follow that these conditions are more lethal in treated patients, and that, in spite of more " recurrences ", progression of ischæmic heart-failure did not occur in the untreated group.

With regard to the overall figures for mortality, they are all within expectation, and even the 91% five-year survival in the " refined " treated group has been duplicated in highly selected patients who have made a complete symptomatic and electrocardiographic recovery (Master et al.[3]) In Thomes et al.'s total series only 32% are documented as having abnormal electrocardiograms and further selection may have reduced this proportion.

My grave doubts on the efficacy of long-term anticoagulant prophylaxis are further reinforced by the careful study of Hilden et al which you published last week. The small gain from the prevention of venous thrombosis and embolism seems to be balanced by other hæmorrhagic risks of the treatment, the authors being quite unconvinced of its value even in acute infarction.

I share with many colleagues both their desire to help patients liable to arterial occlusion and their disappointment with the results of so much rationally planned endeavour. Appreciation of inadequacy of our therapeutic efforts should at least encourage research in new directions.

Evidence on the therapeutic efficacy of anticoagulant treatment of arterial occlusion seems to be quite inadequate. The Danish report seems to contraindicate its use under any circumstances other than strict hospital control, and before we accept long-term anticoagulants which would cost millions in cash and more in misery we should certainly wait for more adequate evidence. No follow-up of the Medical Research Council's investigation has yet appeared; but possibly we may expect to see their later evidence before long. Meantime I remain incredulous but not uncritical.

Postgraduate Medical School, London, W.12. JOHN MCMICHAEL.

1. McMichael, J., Parry, E. H. O. *Lancet*, 1960, ii, 991.
2. Thomes, A. B., Scallen, R. W., Savage, I. R. *J. Amer. med. Ass.* 1961, **176**, 181.
3. Master, A. M., Jaffe, H. L., Teich, E. M., Brimberg, L. *ibid.* 1954, **156**, 1551.

ANTICOAGULANTS IN ACUTE MYOCARDIAL INFARCTION

SIR,—The assessment of the value of short-term anticoagulant treatment in myocardial infarction must be entirely objective. A trial of such treatment should involve approximately equal numbers of treated and control patients. There should be some way of randomly distributing the cases to the two different groups, and this should be adhered to strictly throughout the study. The groups should be similar with regard to age, severity of disease, presence of recurrent infarction, associated diseases, period from onset, supportive therapy, and social grades. Anticoagulant treatment must be shown to have been appropriate and effective where administered.

Though few studies favouring anticoagulant drugs would satisfy even the majority of these criteria, where results such as those described last week by Dr. Hilden and his colleagues are in opposition to the accepted views and majority findings, they must be able to satisfy reasonable criticism. But their trial obviously does not satisfy the criteria mentioned above.

With regard to anticoagulant administration, most investigators have found that the results with subcutaneous heparin are poor; and dicoumarol, although giving useful results, has generally been discarded because of its slow action. Certainly it is necessary to show that better results could not have been obtained with more modern therapy.

The main criticism must be, however, that the results and conclusions, even if valid, cannot be applied to Britain and the United States, where different systems of control of anticoagulant dosage are generally used. Hilden et al. controlled treatment with Owren's prothrombin and proconvertin (P & P) test. In most countries outside Scandinavia the Quick prothrombin-time is used to control treatment. It has been shown [1] that the Quick prothrombin activity of 15–30% using acetone-human-brain thromboplastin represents a much greater depression of coagulability than 10–30% with the P & P test. (This applies using both saline dilution curves and dilution curves with alumina plasma in the Quick procedure.[2]) Readings as high as 55% and 60% were occasionally observed when the P & P result was less than the 25% which was taken as the upper limit of the therapeutic range by the Danish workers.[2] Even so, excellent results have been obtained in Scandinavia using the relatively mild depression of coagulability obtained with the P & P test; and the possibility cannot be excluded that faulty reagents or technique are the cause of the poor results in the Danish hospitals.

Hilden et al. are entitled to draw several conclusions from their careful investigation. They could conclude that anticoagulant treatment for myocardial infarction in their own two hospitals is valueless, or that the combination of subcutaneous heparin and dicoumarol is ineffective, or even that depression of coagulability to 10–25% with the P & P test is insufficient; but they cannot validly assume that treatment given elsewhere for myocardial infarction is not worth while.

The weight of medical opinion is so against this that a short-term trial of anticoagulant treatment in myocardial infarction involving large numbers of untreated patients, even if morally justifiable, would be physically impossible in most hospitals in Britain. Hilden et al. seem to have been confused by the number of statements of disbelief in the anticoagulant treatment of myocardial infarction in the medical literature recently, even though the majority

1. Lempert, H., Poller, L. *Lancet*, 1960, ii, 1115.
2. Poller, L. Unpublished.

were statistically unacceptable. Surely this results from the fact that the medical journals have been assuring us of the value of anticoagulants since the early 1940s, and it is only reports such as those from Copenhagen which now still arouse our curiosity.

Withington Hospital, Manchester. L. POLLER.

TAKING THE NURSING OUT OF NURSING

SIR,—It was with interest and chagrin that I read Mr. Bryan Jennett's article (July 8).

Mr. Jennett stated that he was reporting what he saw out of the corner of his eye. It is too bad that he did not open both eyes wide so that a less distorted and one-sided view of nursing practice and functions could have been observed with more perspective.

He states that patients are given menus from which they make selections and that, without the advice of a nurse, patients make unwise choices and if slightly confused will order most curious diets which lead to a considerable waste of food. In reality, menus given to a hospital patient list the foods he may have if he so desires. Why should a nurse be expected to advise a patient on what he should order? Certainly, with confused patients, advice may well be given by the dietitian or some member of the nursing staff. Where selective menus are used, there is usually considerably less waste of food.

Mr. Jennett's observation on communications between the nurses and doctors must be unique. In twenty years of nursing in several States I have never encountered a group of women who could not and/or would not talk to a member of the opposite sex—regardless of his profession or vocation!

The account of the conference which Mr. Jennett attended on administration and supervision intrigued me. It seems that the informal setting where nurses met *as equals* with members of other professions was disquieting to the author, to say the least. He says: "For three days these men of distinction, in their sport shirts, lived with this formidable group of women, similarly informally dressed, and a lot of ground was covered before the final barbecue on the beach." I have only one question to ask: Were there any male survivors other than the author after the "final barbecue on the beach"?

The author mentions the "curious attitude" nurses have toward doctors. He attributes this to the quest for improved status. I do not agree with this. The nursing profession here has realistically faced the fact that we do not have and cannot teach and train the quantity of professional nurses needed for the health professions. The nursing profession has tried to determine the functions that should be done by the professional nurse and those that can be effectively and safely done by practical nurses and aides. As a result of this, there has been a shift (and not quest) in the status and role of the professional nurse. Many physicians, including Mr. Jennett, find this emerging role disturbing. No longer are nurses "hand-maidens" of the physician, subject only to his command and direction. We are striving toward a partnership role with other health professions. We have had to undergo and forgo changes in our role conceptions and the physician is going to have to accept these. The doctor is still the leading member of the health team and is not considered, hierarchy-wise, just above the janitor!

I think it is important that our countries have an opportunity to get an "inside picture" of our professions. I do hope that future articles will not be written from such limited experiences as Mr. Jennett depicts.

Indianapolis, Indiana, U.S.A. HELEN KOLDJESKI.

LOCAL-HEALTH-AUTHORITY CLINICS

SIR,—The Minister of Health stated in the House of Commons on July 11 that he had recommended the prescription charge as an additional source of revenue which could be used to good effect elsewhere in the health service. It seems that any increased costs of improving the service would be met by increased charges to the patient and by less from the Exchequer. Before the already overtaxed patient is asked for more it is right that we should examine the present structure to ensure that there is no wastage of either medical manpower or money.

The general practitioner has undertaken to render all proper and necessary treatment to his patients under the Act. The antenatal and child-welfare clinics relieve some doctors of their responsibility at a cost to the taxpayer of £10 million a year. Dr. Roberts (Aug. 12) submits that "whatever action is taken must be on realistic lines". The closing of these clinics at the present time of national financial difficulty is, in my opinion, regarding things in their true nature and dealing with them without being bound by prejudice and convention.

Liverpool. G. E. CRAWFORD.

CONVERSION OF ST. EBBA'S?

SIR,—I should like to comment on your annotation last week about the proposals to convert St. Ebba's Hospital for the use of mentally subnormal patients.

My own suggestion is that, rather than convert the whole of St. Ebba's, or any other hospital, for use by mentally subnormal patients, hospitals already in existence for the mentally ill should open up departments for the subnormal. I have been interested in the lack of objection to such a suggestion so far as I have had the opportunity of discussing it. I suggest that this proposal, together with the whole problem of the future of St. Ebba's, be studied by a few experts in the relevant fields before any definite steps are taken.

St. Ebba's Hospital, Epsom, Surrey. W. M. MCINTYRE.

HYPOPHOSPHATÆMIA IN GOUT

SIR,—In response to the observations of Professor de Oliveira and Dr. Laus-Filho (July 22), we have analysed the serum-phosphate levels of 10 patients (9 men and 1 woman) with primary gout without evidence of renal disease attending the gout clinic at Hammersmith Hospital.

Their gout had lasted from a few months to over twenty-five years. In all the serum-urea was normal (< 45 mg. per 100 ml.)[1,2]; so were calcium, alkaline-phosphatase, and protein patterns. There was no evidence of blood dyscrasia, other than an iron-deficiency anæmia in 1 patient. In each patient the serum-uric-acid was 6·5 mg. per 100 ml.[3,4] or over at the time of investigation. All phosphate levels[5] were estimated before starting, or at least one month after finishing, uricosuric therapy. 10 normal subjects (9 men and 1 woman) served as controls.

Serum-phosphate levels (mEq. per litre) were: in patients with gout, 1·4, 1·7, 1·8, 1·9, 1·9, 2·0, 2·1, 2·2, 2·3 (men), and 2·1 (woman); and in normal subjects, 1·9, 2·0, 2·0, 2·2, 2·2, 2·4, 2·4, 2·5, 2·5 (men), and 2·1 (woman).

Thus the average level for our normal subjects was 2·22 mEq. per litre (S.D. 0·221). Only 2 of our 10 patients with gout had levels less than two standard deviations below the normal average, and the difference for the group is not statistically significant. Elsewhere[6] a range for 80% of normal people is cited as 1·7–2·4 mEq. per litre with a 100% scatter to 1·4–2·6 mEq. per litre. All our 10 patients with gout would fall within normal limits in this latter range.

It seems unlikely to us that hyperuricæmia by itself will produce a renal tubular defect of phosphate transport.

Department of Medicine, Postgraduate Medical School, London, W.12. A. ST. J. DIXON F. M. MCCALLUM.

1. Skeggs, L. T., Jr. *Amer. J. clin. Path.* 1957, **28**, 311.
2. Marsh, W. H., Fingerhut, B., Kirsch, E. *ibid.* p. 681.
3. Henry, R., J., Sobel, C., Kim, J. *ibid.* p. 152.
4. Caraway, W. T. *ibid.* 1955, **25**, 840.
5. Fiske, C. H., Subbarow, Y. *J. biol. Chem.* 1925, **66**, 375.
6. King, E. J., Wooton, I. D. P. Micro-Analysis in Medical Biochemistry. London, 1959.

WHERE ARE THEY TO GO?

SIR,—Your annotation (Aug. 5) is most apt at the present time.

The atmosphere of the modern mental hospital should approximate as far as possible to that of the outside world. Only in exceptional cases of severe psychosis need any restrictions be placed upon the freedom of the individual. It is because of this new atmosphere that is prevailing in most hospitals that the fear of mental illness is declining and that patients, coming earlier for treatment, find their stay as pleasant if not more so than in a general hospital and do not object to a return visit. This new freedom must not be lost for the sake of a few psychopaths. These people must not be admitted to an ordinary psychiatric hospital, where they derive no benefit for themselves, cause tension and upset to the other patients, and waste the time of hard-pressed medical and nursing staff. Whilst the Mental Health Act is right to regard them as sick people, there is as yet no generally recognised and effective treatment that can be made available to them in the mental hospital. The few specialised units that do exist are quite inadequate and largely experimental.

I would suggest therefore that what is wanted is more prisons like hospitals rather than hospitals like prisons. In a field of inspired guesses rather than rational treatment, it would seem that Herstedvester is the sort that is likely to produce the best results. Until we have such places staffed by the right people the psychopath is better off in prison, where he can do the least harm to the smallest number of people.

The Towers Hospital, Leicester. H. B. KIDD.

TEACHING PSYCHIATRY TO UNDERGRADUATES

SIR,—The communication by Dr. Garmany and Dr. Whiteley (July 1) is of great interest and importance.

The students' answers get at the core of the matter. It is clear that most teachers in the undergraduate schools appreciate the widening interest and awareness of the students in all the mental-health, mental-illness, and mental-subnormality aspects of their clinical studies. Of all this we hope that much which the authors advocate in the teaching of everyday psychiatry will grow, develop, and become commonplace. But this stimulation of the undergraduates' minds in this direction should be followed up by prospective general or family medical practitioners doing post-registration resident appointments in the hospitals for mental illness or mental subnormality. The demands (as envisaged in the Mental Health Act) for early diagnosis, domiciliary care, and closely integrated functioning in the medical, social, and occupational spheres will require doctors to know more and more about general psychiatry. Everything must be done to get this over to the undergraduates and the younger doctors. It is up to us to point this out to them.

In the meantime, it is important that the hospitals should provide really good residential accommodation (for the single or married) and facilities, and keep pressing the regional boards and management committees to see to it. If each hospital or hospital group will move towards providing a quiet study-room, discussion periods, a moderate library, clinical seminars and conferences, and a good teaching plan for the juniors there is little doubt that more applications will come in for these posts. The postgraduate follow-up of the good undergraduate teaching will then have an enormous benefit in our N.H.S. When and where we have better integration between general hospitals and mental hospitals there should develop increasing opportunities for rotating junior appointments. My own view is that a young doctor who has had the sense to do a 6 or 12 months' post in clinical psychiatry is going to be a much better family practitioner. Moreover, with the present experience available in day-hospitals, acute wards, short-stay mental illness, and special therapy, and the shift away from any static attitudes to mental disorders, the junior will find a most interesting experience—one which should give him or her greatly increased confidence in domiciliary and community care.

Whether or not the junior resident proceeds to a D.P.M. is another matter and will depend upon the individual. In any case, we hope to see many more general practitioners with the D.P.M. The students' answers to item 9 in Dr. Garmany's questionnaire—"Does psychiatry attract you as a career?"—is truly a fine example of the mixed attitudes in the minds of medical students. It would be interesting to see what answers they would give after a 6-month resident appointment in a good department or hospital for mental illness. Some students might even thus proceed from an "average intellect" to a "first-rate mind"!

Department of Child Health, University of Bristol. A. V. NEALE.

MUMPS 1961

SIR,—The mention in your annotation (June 24), on the present epidemic of mumps, of some of the less common complications prompts me to report an unusual case I have recently seen.

A man of 59 became acutely ill three days after the onset of bilateral parotid swelling. Bilateral pain and swelling of the testicles, vomiting, and weakness of the voice developed. This last symptom persisted; and when he got up, two weeks after the onset, he noticed that he was unusually short of breath. Examination then revealed a complete left recurrent laryngeal paralysis. He was referred for a chest examination, and his left diaphragm was found to be paralysed. There was no other clinical or radiological abnormality; and results of bronchoscopy were normal. It seems most unlikely, therefore, that any coincidental bronchial neoplasm or aortic aneurysm was causing the two paralyses.

Meningoencephalitis is the commonest neurological complication of mumps; but various peripheral neuropathies confined to one or more nerves are described. Even paralytic poliomyelitis may be simulated.[1 2] In a comprehensive review, Miller et al.[3] record only one case with laryngeal involvement and none with diaphragmatic paralysis. An earlier review [4] does not mention laryngeal paralysis; but it refers to a single instance of diaphragmatic paralysis, which was bilateral, in a fatal case of tetraplegia. In these cases with single nerve lesions, complete recovery is usual.[1 3]

In the patient I have described, the left diaphragm is beginning to resume normal movement, fourteen weeks after the onset of mumps, but the larynx remains paralysed.

Milford Chest Hospital, Godalming, Surrey. A. S. HERINGTON.

DISPOSABLE FILTER FOR MELROSE HEART-LUNG MACHINE

SIR,—Dr. Atherstone's report (July 22) of a disposable blood filter prompts a description of a similar piece of apparatus which was, for a time, successfully used in this unit for filtering blood into the reservoir of the Melrose heart-lung machine.

A piece of 3 mm. metal rod was bent to form seven-eighths of a circle whose diameter was 2 cm. greater than the outside diameter of the reservoir. This formed the support for the conical nylon filter, the circular edge of which was punched at intervals with an ordinary leather punch, and the support then threaded in and out of the holes so punched. This provided for ready renewal of the filters before sterilisation for each case.

1. Donohue, W. L., Playfair, F. D., Whitaker, L. *J. Pediat.* 1955, **47**, 395.
2. Lenette, E. H., Caplan, G. E., Magoffin, R. L. *Pediatrics*, 1960, **25**, 788.
3. Miller, H. G., Stanton, J. B., Gibbons, J. L. *Quart. J. Med.* 1956, **25**, 467.
4. McKaig, C. B., Woltman, H. W. *Arch. Neurol. Psychiat.* 1934, **31**, 794.

I was indebted to my wife for the suggestion about suitable disposable filters, and, after a furtive visit to Marks & Spencers, reservoir in pocket, and withstanding the embarrassment of an initial explanation, these were readily available—the functional half unit of a nylon brassiere. The purchase price was 5*s*. for two filters. Subsequently it became possible to obtain the relevant portions before attachment to the remainder of the garment, unadorned by embroidery which obstructs the flow of blood in bulk quantity, from the manufacturers. The fact that the periphery is not a true circle is of no importance. They were readily sterilised by autoclaving, each threaded on to a ring, and this practice was only discontinued when it was found unnecessary to submit the blood to further filtration beyond that of an ordinary transfusion filter in the bottle. The most appropriate size of "filter" for this purpose is a 36 in. medium cup.

King Edward VII Memorial Chest Hospital, Hertford Hill, near Warwick. J. C. A. RAISON.

SAFETY IN X-RAYS?

SIR,—In an editorial on Perinatal Mortality you wrote [1]: "Radiography can be an invaluable aid in diagnosis and prognosis; but, remembering the work of Stewart et al., radiographs should not be taken needlessly." This is grammatically unsound and morally wrong. For the grammar refer to Fowler [2] on "unattached participles". There is no authority on the morality, but your interpolation of the fearsome phrase "remembering the work of Stewart et al." comes close to Gamesmanship—i.e., The Art of Winning Games Without Actually Cheating (Potter [3]). With nice subtlety you have injected a fear of radiation totally irrelevant to the discussion. Such a phrase from your influential pen promotes fear and guilt in doctors and in parents, and delays and impedes X-ray investigations. Uninfluenced by contact with patients, you have no personal experience of the consequent suffering, nor do you daily have to summon the courage to take the extra radiographs that make the difference between an indifferent and a thorough examination. That you should have accepted, to this extent, a preliminary report that had been much criticised shows a lack of healthy conservatism; that you should have used it as a basis for propaganda seems to be improper.

The work of Stewart et al.[4 5] on the hazards of diagnostic radiation has become probably the most quoted work in medical writing, and Dr. Stewart [6] intends to make further use of the methods and material on which it is based. Yet there appears to be a curious paradox in the fundamental analysis of the material—i.e. in table II of the 1958 report.[5] The relevant information is summarised in the accompanying table I. The ratio 0·90 is not significant in the sense that it does not mean that the risk of malignancy is decreased by a factor of 0·88 by radiation, but the 3 ratios *differ significantly from each other*. This can be interpreted to mean only that the post-nuptial prezygote is protected from the noxious effects of radiation, presumably either by the sanctity of the marriage certificate, or by some obscure metabolic change due to marriage. Dr. Stewart [7] has hinted that the differences between these ratios might be important, but as her thesis is based on these ratios a hint is not enough; the paradox merits a full and lucid explanation.

You have conceded that the study of Court Brown et al.[8] does not support the hypothesis that antenatal X-rays double the risk of leukæmia. It appears to refute this hypothesis. If the hypothesis were true the expected number of cases in this series of 40,000 children would be 20, and the chance of their finding 9 cases, as they did, is less than 1:300.[8] Of course $P < 10^{-7}$ seems more significant than $P < 1:300$, but "The question is," as Humpty Dumpty said, "which is to be Master—that's all."

TABLE I—SUMMARY OF RELEVANT DATA FROM STEWART ET AL.[5]

Stage of life exposed	No. of children with history of antenatal X-ray exposure: Cases of childhood malignancy	Controls	Case/control ratio	Statistical significance	Multiplier factor for risk of malignancy
Ante-nuptial prezygote	44	26	1·69	Technically significant $P < 0·05$	1·74
Post-nuptial prezygote	109	121	0·90	Not significant (occurs by chance)	0·88
Zygotic (i.e., fœtal)	178	93	1·91	Highly significant $P < 10^{-7}$	2·1

Table II shows that of 64,000 children subjected to antenatal X-rays, 18 developed leukæmia, and not 21 as expected or as in the control children. This does not mean that small doses of X-rays protect from the normal hazard of leukæmia, but it does seem to indicate that they do not add to the risk. The risk is certainly not doubled.

It can thus be concluded that:

(1) There is no evidence that diagnostic antenatal irradiation doubles or otherwise increases the risk of childhood malignancy.

(2) If there is a risk (in spite of the lack of evidence thereof) it could not be detected in surveys of 64,000 pelvimetries.

(3) As the fœtus is considered to be at the most sensitive stage of life, the absence of a demonstrable risk from the relatively large whole-body doses in pelvimetries precludes any measurable risk from ordinary doses after birth.

(4) As diagnostic doses today are far less [9 10] than those used at the time the survey children were exposed, the undetectable risk, if there is a risk, is correspondingly reduced.

TABLE II—INCIDENCE OF LEUKÆMIA AND/OR CANCER IN CHILDREN IRRADIATED IN UTERO COMPARED WITH EXPECTED INCIDENCE

Authors	Irradiated fœtuses	Cases of malignancy	Expected or control cases
Court Brown et al.[8]	39,166	9	10·5
Lewis [11]	4291	1	2·4
McMahon [12]*	17,300	8	8
Rabinowitch [13]	4000	0	1
Totals	64,000	18	22

* Calculated from quoted figures.

The time has come for you to try to remove the fear you have helped to create. Please begin by publishing this letter under the heading Safety in X-rays rather than your usual Radiation Hazards.

Johannesburg. HARRIS JACKSON.

***Though Dr. Jackson has plainly caught us with our participles unattached in 1958, we were otherwise less vulnerable than he suggests. We said that "radiographs should not be taken needlessly"; and whatever estimate may finally be put on the findings of Dr. Stewart and her colleagues, there remain excellent reasons for sticking to this advice. Last December's report from the Adrian Committee (though concerned mainly with measuring the genetic impact of medical irradiation) had this to say about X-raying pregnant women: "Only essential examinations should be carried out during pregnancy,

1. *Lancet*, 1958, i, 627.
2. Fowler, H. W. A Dictionary of Modern English Usage; p. 674. London, 1952.
3. Potter, S. A Book of Wit and Humour; p. 243. London, 1960.
4. Stewart, A., Webb, J., Giles, D., Hewitt, D. *Lancet*, 1956, ii, 447.
5. Stewart, A., Webb, J., Hewitt, D. *Brit. med. J.* 1958, i, 1495.
6. Stewart, A. *ibid.* 1961, i, 507.
7. Stewart, A. *ibid.* p. 452.
8. Court Brown, W. M., Doll, R., Bradford Hill, A. *ibid.* 1960, ii, 1539.
9. Ardran, G. M., Crooks, H. E. *Brit. J. Radiol.* 1957, **30**, 295.
10. Fainsinger, M. H. *Med. Proc.* 1957, **3**, 422.
11. Lewis, T. L. T. *Brit. med. J.* 1960, ii, 1551.
12. McMahon, B. Paper read to the American Public Health Association (1958) Quoted by Court Brown et al.[8]
13. Rabinowitch, J. *Brit. med. J.* 1958, ii, 796.

and particular care should be taken to avoid irradiation of the fœtus whenever possible. In all women of childbearing age the clinician requesting the examination should never overlook the possibility of early pregnancy".[1] —Ed. L.

HYPOPROTEINÆMIA

SIR,—Your leading article (Aug. 5) was a valuable review of the advantages and disadvantages of the various methods for studying gastrointestinal protein loss. However, it should be emphasised that these methods are only semiquantitative, and do not differentiate between the ^{131}I-albumin catabolised in the bowel and that catabolised in the body.

^{131}I-P.V.P. (polyvidone) is unsuitable for this purpose because structurally it is unlike albumin. ^{51}Cr-albumin is also unlikely to be suitable for turnover studies,[2] as it seems from the high urinary excretion of the label over four days that the protein is either denatured or the label is only loosely bound.

The chief difficulty in studying the catabolism of ^{131}I-albumin in the bowel is to prevent the reabsorption of the ^{131}I liberated by the digestion of albumin. This difficulty has been overcome by a method devised to study the gastrointestinal ^{131}I-albumin loss while concurrently estimating turnover.[3] In this method the reabsorption of ^{131}I is prevented by feeding an ion-exchange resin by mouth. The resin binds the iodinated digestion products of ^{131}I-albumin, and by counting the fæces protein loss can be estimated.

We have found this method more sensitive than ones based on ^{131}I-P.V.P. With it, the amount of albumin catabolised in the gastrointestinal tract can be measured separately from that catabolised in the body. We have found this distinction useful in studying the results of treatment in protein-losing enteropathy.

West Middlesex Hospital, Isleworth, Middlesex, and Postgraduate Medical School of London, London, W.12. K. N. JEEJEEBHOY.

ADMITTING SCHIZOPHRENIC MOTHERS WITH THEIR BABIES

SIR,—I have read with interest the article by Dr. Baker and his colleagues (July 29).

The authors describe a series of 20 schizophrenic patients admitted with their babies to the unit. The criteria for diagnosis are not stated, nor whether patients with associated affective disturbances are included or excluded. The exact inpatient treatment given to this group of 20 patients is not at all clear; but it is stated that chlorpromazine was often continued after discharge. The results are compared with a control group of 20 patients selected from an earlier unstated period of time. The inpatient treatment given to this group is not mentioned, nor whether any outpatient therapy was continued. In the assessment of results, emphasis is laid on the ability of the mother to look after the baby after discharge. This ability, however, is not necessarily related to the degree of psychiatric improvement, particularly in primiparæ. Baker et al. point out that the average length of stay in hospital was 10·8 weeks for patients in the unit, compared with 16·8 weeks for the control group. It is known that the average length of stay in psychiatric hospitals has been steadily decreasing during the past few years. That the period in hospital differed in the two groups could, therefore, be due to this fact alone. I would suggest that the defects stated above invalidate any claims about the therapeutic value of admitting the baby with the schizophrenic mother.

The authors state that many psychiatrists consider that puerperal schizophrenia carries a bad prognosis. This is not generally believed today. In a retrospective study of cases admitted to St. Patrick's Hospital, Dublin,[4] I found that, of 15 patients with puerperal schizophrenia, 6 were discharged as "recovered" and 9 as "much improved" after an average stay in hospital of 12·4 weeks. At follow-up (average 4$^1/_2$ years later, range 4 months to 11 years) all 15 patients were in normal health. A group of 29 cases of schizoaffective psychosis also responded well to treatment. These results seem at least as good as those obtained by Baker et al. in either of their groups.

Dr. Baker and his colleagues will need to present further evidence before their views can be accepted.

St. Patrick's Hospital, Dublin. MARY E. MARTIN.

1. See *Lancet*, 1960, ii, 1292.
2. Waldmann, T. A. *Lancet*, July 15, 1961, p. 121.
3. Jeejeebhoy, K. N., Coghill, N. F. *Gut*, 1961, **2**, 123.
4. Martin, M. E. *Brit. med. J.* 1958, ii, 773.

THE N.H.S. UNNECESSARY?

SIR,—The Jewkeses have written an interesting pamphlet, and I hope they will follow it up with a detailed survey of medical administration. The N.H.S. has brought to something near perfection the technique of killing a cat by choking it with cream. For example:

(1) Health centres were proposed. Ridiculously lavish standards were then set. It was impossible to find the money, so there are no centres, in most places, instead of modest ones.

(2) A hospital management committee proposes a small plan of improvement costing, say, £2000. The regional board suggests a much more elaborate plan, costing £20,000. Unfortunately there is not £20,000 to spare, so nothing at all is done.

Maldon, Essex. D. CARGILL.

LESSENING THE HANDICAPS OF CHILDREN

SIR,—Dr. Heaton-Ward (Aug. 5) suggests that if the National Spastics Society and the National Society for Mentally Handicapped Children joined forces under a new name, children and their parents would benefit.

Specialisation and union have advantages and disadvantages. That many spastics are mentally handicapped does not prove or disprove that it would be better to have one society. In seeing handicapped children we try to assess their capacities, their handicaps, and their needs, both of further investigation and of treatment and rehabilitation. In each child the motor, sensory, speech, epileptic, intellectual (global and specific), emotional, and social handicaps are assessed. Would the children gain if *all* the various specialised voluntary societies fused into one? Some of the drive of individual workers might diminish.

Dr. Heaton-Ward's suggestion derives from the fact that at present "spastics" have become respectable, while mental defectives are still often poorly thought of. But the change in attitude to spastics has taken place over the past ten years and the attitude to the intellectually handicapped is improving largely because of greater understanding—the result of public education by doctors, television, &c. In a few more years the public will come to understand more clearly the interrelationship of the two types of handicap. Understanding in the medical profession has similarly improved. I do not think it is only the doctors in hospitals for the mentally subnormal that look at each child as a total problem. There are good and less good doctors in all branches of medicine.

Dr. Heaton-Ward says that the two societies seem to pursue separate existences; their activities are, in fact, not so distinct. The National Spastics Society has its psychologists and is considering how it can promote research on psychology in childhood. The Pædiatric Research Unit endowed by the National Spastics Society is contributing to the study of the origins of mental deficiency, and of the special psychological problems of learning in cerebral-palsied children.

The professional journal published by the National Spastics Society, the *Cerebral Palsy Bulletin*, publishes articles on general aspects of mental handicaps, as well as those related to cerebral palsy.

Cooperation could be improved, though it is not absent between individuals and bodies interested in spastics and those interested in the mentally handicapped.

But the fields are not identical. Now the National Spastics Society is joining forces with the British Council for the Welfare of Spastics. Personally, I doubt whether it would be advantageous to handicapped children and their families if the National Spastics Society and the National Society for Mentally Handicapped Children were to join forces at this time.

London, S.W.1. R. C. MAC KEITH.

THE ENCEPHALOGRAM AS A MONITOR OF STATUS EPILEPTICUS

SIR,—I have read with interest the article by Dr. James and Dr. Whitty (July 29). I was surprised to see no mention of the effectiveness of a dilute thiopentone intravenous drip in stopping the fits when other methods, short of curarisation, have failed.

I was asked to see a hypertensive woman of 54 who had had a right hemiplegia two years previously and was in hospital for rehabilitation. During her stay, status epilepticus developed; and, though she had received gr. 27 of phenobarbitone sodium, 80 ml. of paraldehyde, and 750 mg. of phenytoin sodium intramuscularly over the preceding four days, her fits remained uncontrolled. A dilute thiopentone drip (0·5%) was then set up with an initial drip-rate of about 60 drops per minute. This was subsequently slowed to about 20 drops per minute when the fits were abating. After one pint had been infused, the drip was discontinued. The fits ceased within an hour of starting the drip and did not recur. The patient gradually improved and became rational five days later.

In an earlier case associated with eclampsia and hyperpyrexia, a dilute thiopentone drip again proved effective in stopping the fits when routine medical therapy had failed; but on this occasion it was combined with surface hypothermia. This patient subsequently recovered completely and had no further fits.

Department of Anæsthetics,
Royal Infirmary,
Aberdeen. W. N. ROLLASON.

GENETIC FACTORS ON THE X CHROMOSOME

SIR,—Dr. Stewart in his letter of Aug. 5 on this subject expresses the opinion that the appearance of heterozygotes for sex-linked genes in man is unfavourable to the hypothesis [1] that only one X chromosome is active in the body-cells of normal female mammals. In fact, this evidence is favourable.

The hypothesis predicts that in a human female heterozygous for a sex-linked gene, some of the relevant cells will have a gene activity equal to that in a normal male or homozygous female, and the remaining cells will have an activity equal to that of the mutant male (or homozygous female, if known). The exact proportions of the two types of cells will vary by chance, as the result of the random inactivation of one X chromosome or the other early in development. Thus in cases in which the results of gene activity can be measured quantitatively, the value for heterozygotes would be expected to be intermediate, and variable. This is the case for glucose-6-phosphate-dehydrogenase deficiency.[2] Similarly, for hæmophilia A and Christmas disease, laboratory measurements of antihæmophilic globulin and plasma-thromboplastin component sometimes, but not always, give intermediate values for heterozygotes.[3 4] When the results of gene activity can only be recognised as normal or abnormal, heterozygotes will be expected to show partial or occasional manifestation of abnormality, or both. When the manifestation is occasional its frequency will depend on the proportion of relevant cells that must be abnormal to give an abnormal phenotype. A study [5] of the literature shows that sex-linked genes with partial expression in heterozygotes include choroideremia, keratosis follicularis, anhidrotic ectodermal dysplasia, chronic hypochromic anæmia, vitamin-D-resistant rickets with hypophosphatæmia, and diabetes insipidus. In some of these the expression is only occasional, and in all it is variable. Conditions with occasional manifestation in heterozygotes include retinitis pigmentosa, nystagmus, night-blindness, and megalocornea, while rare complete manifestation has been claimed for colour-blindness, hæmophilia, Christmas disease, anhidrotic ectodermal dysplasia, and Duchenne-type muscular dystrophy. Only one sex-linked condition—ichthyosis vulgaris—is not known to have any heterozygous effect.

Thus the hypothesis will explain the heterozygous effect in colour-blindness referred to by Dr. Stewart, also the variability of this effect; and the rarity of typically colour-blind heterozygotes merely shows that a woman can still distinguish colour when only a small proportion of her cones have the normal gene acting.

M.R.C. Radiobiological Research Unit,
Harwell, Didcot,
Berks. MARY F. LYON.

1. Lyon, M. F. *Nature, Lond.* 1961, **190**, 372.
2. Beutler, E. *Blood*, 1959, **14**, 103.
3. Biggs, R., Macfarlane, R. G. *Brit. J. Hæmat.* 1958, **4**, 1.
4. Pitney, W. R., Dacie, J. V. *Brit. med. Bull.* 1955, **11**, 11.
5. Lyon, M. F. Unpublished.

ACUTE LEUKÆMIA AND KLINEFELTER'S SYNDROME

SIR,—Prompted by the communication from Mr. Mamunes and his colleagues (July 1), reporting the association of acute leukæmia and Klinefelter's syndrome in the same patient, we wish to report preliminary findings from another patient.

In the course of a cytogenetic survey of primary bone-marrow disease, chromosome studies were performed in January, 1961, on specimens of peripheral blood and bone-marrow from a man of seventy-three. He had first attended St. George's Hospital in October, 1959, complaining of abdominal discomfort and flatulence; physical examination revealed considerable hepatosplenomegaly. Investigation of the peripheral blood showed leucoerythroblastosis with hæmoglobin 9·1 g. per 100 ml. (62%), white blood-cells 12,700 per c.mm., platelets 335,000 per c.mm., and reticulocytes 3·8%; myelocytes and metamyelocytes were seen, together with 50 nucleated red blood-cells per 100 white blood-cells and slight red-cell hypochromia. A bone-marrow specimen comprised almost exclusively erythroblasts and basophilic normoblasts with some bizarre mitoses; but there was no evidence of megaloblastic change. The erythroblast cytoplasm did not contain *p*-aminosalicylic-acid-positive material.[1] The alkaline-phosphatase activity of the granulocytes in the peripheral blood was scored as 94, this being at the upper limit of normal.[2] The absence of iron-containing granules in the erythroid precursors excluded any sideroblastic achrestic state. Tests of liver-function were normal. A tentative diagnosis of chronic erythræmic myelosis was made. Blood was transfused and iron given.

During the subsequent months the anæmia, which necessitated further transfusion, and the leucoerythroblastosis persisted, although granulocyte precursors, occasionally including myeloblasts, became more numerous than the nucleated red cells in the peripheral blood. A second marrow specimen in August, 1960, showed reduced overall cellularity with considerably less erythropoietic activity. Subsequent marrow punctures in January and May, 1961, demonstrated overactivity of the granulocyte series, with an increase of early forms, in a very cellular specimen, the red-cell precursors being much less numerous than in the first marrow specimen. The findings in August, 1960, were probably due to an unrepresentative specimen.

The patient complained of diarrhœa with rectal hæmorrhage; this, due to bleeding hæmorrhoids, was so severe that emergency transfusion was required. In January, 1961, when the initial

1. Quaglino, D., Hayhoe, F. G. J. *Brit. J. Hæmat.* 1960, **6**, 26.
2. Hayhoe, F. G. J., Quaglino, D. *ibid.* 1958, **4**, 375.

RESULTS OF CHROMOSOME COUNTS ON SPECIMENS OF PERIPHERAL BLOOD AND BONE-MARROW

Tissue	Date (1961)	No. of chromosomes							Total
		<44	44	45	46	47	48	>48	
Bone-marrow	Jan. 16	5	..	..	5	28	2	..	40
,, ,,	May 15	..	..	..	1	20	..	..	21
Peripheral blood	Jan. 24	..	..	..	..	11	..	..	11
,, ,,	March 13	2	..	..	1	49	..	..	52
,, ,,	May 15	..	..	..	1	10	..	..	11
Total cells examined ..		..	..	..	..	..	..	..	135

chromosome studies were carried out, he had also developed steatorrhœa for which, as yet, no definite cause has been found, and the response to a gluten-free diet cannot yet be judged.

Chromosome Studies

The findings from specimens of peripheral blood and bone-marrow are shown in the accompanying table. In the peripheral blood there was active division within the first twenty-four hours of culture due to the early granulocyte, and perhaps also early erythroid, elements. Mitoses were also observed after the usual two to three days of culture. There was no significant difference in the results obtained at these various periods of culture.

The chromosomal mode in every culture of each specimen examined was 47. On detailed analysis of 24 of the better metaphases containing 47 chromosomes (see figure) the extra chromosome was seen to fall in the group 6–12 (Denver convention), which includes the X chromosome. No constant abnormality was observed in the non-modal cells.

A buccal-mucosa smear was sex-chromatin negative, and no drumsticks were to be found in 500 neutrophil polymorphs in a peripheral-blood smear.[3] A specimen of skin was cultured by Dr. D. G. Harnden of the M.R.C. Clinical Effects of Radiation Research Unit, Edinburgh, and a normal male karyotype was found. In counts on 30 cells the distribution of chromosomes was as follows: under 44, 0; 44, 1; 45, 1; 46, 27; 47, 1; 48 and over, 0.

Metaphase containing 47 chromosomes: also shown arranged in groups according to the Denver system.

Interpretation of the chromosome findings in this case is difficult. A constant abnormality is present, but precise definition of the additional chromosome is not yet possible. Using various staining techniques we have made unsuccessful attempts to demonstrate sex-chromatin in cells of peripheral blood and bone-marrow present in the in-vitro cultures. Without the additional criterion of sex-chromatin it is impossible to be certain about the X-chromosome complement of these cells. Moreover, control examination of the sex-chromatin of similar leucocytes in culture from known normal females with sex-chromatin-positive buccal smears has similarly yielded inconclusive results. Interpretation of the lack of neutrophil drumsticks in this case is further complicated by a marked " shift to the left " in the neutrophil series in every blood-film examined—the result of the leucoerythroblastosis.

Possibly the sex-chromosome complement of these cells is XXY. In view of the results of the skin culture, this patient exhibits mosaicism between the skin and hæmopoietic tissues. No other tissue has yet been examined; but if these cells are XXY then the presence of such abnormal cell lines is presumably restricted to a few tissues—perhaps only those concerned with hæmopoiesis. There are no clinical stigmata of Klinefelter's syndrome. There is no evidence of gynæcomastia or gonadal dysfunction; the patient has a forty-six-year-old daughter, and his mental capacity has been sufficient for him to maintain himself and his family.

Alternatively, the additional chromosomes may be autosomal and be related solely to the hæmatological disorder. The abnormality is present in both myeloid and lymphoid elements, for in the peripheral-blood cultures after two to three days the chromosome mode is constant at 47. These cells appear to be lymphoid in origin, whilst the mitoses, also with a mode of 47, examined during the initial twenty-four hours of culture are myeloid and, possibly, erythroid. These findings, then, imply a general disorder of the reticulo-endothelial system; the pattern of the disease process in this patient is not characteristic, but it conforms to that of a primary myeloproliferative disorder.

Critical interpretation of these findings is not feasible until it becomes possible to demonstrate sex-chromatin in cultured hæmopoietic cells, or to identify the X chromosome in the dividing cell, or, in cases such as this, to examine other tissues which might possess the same abnormality and be suitable for sex-chromatin analysis.

The ultimate fate of this man may yet provide a precise diagnosis. At the moment all the changes described might result from the marrow dyscrasia alone, and the absence of clinical stigmata of Klinefelter's syndrome would accord with this.

The chromosomal abnormality is so constant and apparently occurs in cells of such dissimilar lineage within the hæmopoietic system that we think the anomaly may well represent a sex-chromosome defect, and thus be another expression of the XXY anomaly associated with a primary marrow dyscrasia.

We are grateful to Dr. Kenneth Robson for permission to refer to the note of this patient, who was admitted under his care.

N. H. KEMP
J. L. STAFFORD
R. K. TANNER.

Hæmatology Department,
St. George's Hospital,
London, S.W.1.

3. Davidson, W. M., Smith, D. R. *Brit. med. J.* 1954, ii, 6.

WHAT MAKES THE PATIENT BETTER?

SIR,—Dr. Meares (June 10), in his very personal communication, has raised a point of great interest and one that is seldom seen in print. Can it be that psychiatric treatment, by whatever means and with whatever intent, operates by providing the conditions necessary for improving sleep?

If effective psychiatric treatment does act by way of the sleep process, would not Yoga or even fortuitous circumstances be capable of producing a good clinical response? Such a sequence would even explain spontaneous remissions, which have puzzled and intrigued generations of psychiatrists. I am well aware that this easy and unorthodox solution will provoke objection. At least one great Englishman, William Shakespeare, is on my side. Granted that sleep is the " balm of hurt minds ", is it unreasonable to presume that lack of sleep—perhaps chronic or accumulated sleep loss—may be the villain in the evolution of some functional psychiatric disorders? Statisticians express concern about the high incidence of these illnesses in our time. May not the development and general use of cheap effective lighting somehow be implicated in the increase in psychopathology?

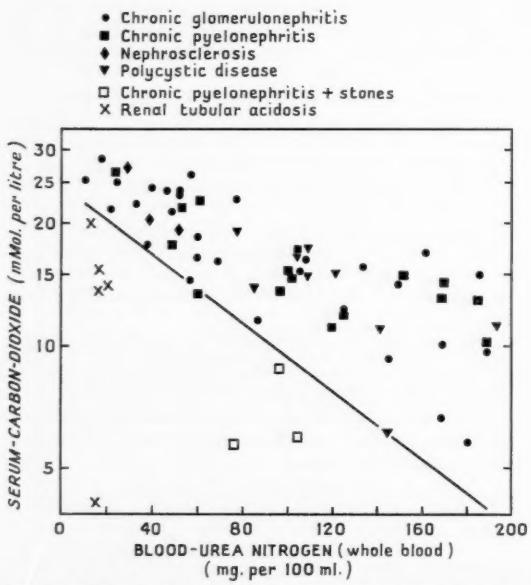
Rollman Receiving Hospital, and
State Institute of Psychiatry,
Cincinnati, Ohio, U.S.A. R. E. KENNEDY.

RENAL TUBULAR ACIDOSIS

SIR,—You discussed three of our papers in your leading article of Jan. 14. We should like to comment on two points.

First, our uncertainty concerning the diagnosis in the 2nd case in our first paper [1] was thought to be well founded. Our initial diagnosis in this patient was osteomalacia due to renal tubular acidosis, but on further reflection we thought that she might equally well have idiopathic vitamin-D-resistant rickets with a secondary chronic pyelonephritis. Since the publication of our papers we have obtained more information on her family history (kindly provided by Dr. L. T. DeWind of Los Angeles, California). Her paternal grandmother had a disease which prevented her walking fully upright; perhaps this was osteomalacia. This does not help us diagnostically. But the patient's mother had renal stones before the age of 42; and, of the patient's 9 siblings, all living, 1 brother aged 66 has renal stones. If the osteomalacia in our patient and the stones in her mother and 1 brother are all due to a similar disorder, the initial diagnosis of renal tubular acidosis now seems the most likely.

1. Elkinton, J. R., Huth, E. J., Webster, G. D., Jr., McCance, R. A. *Amer. J. Med.* 1960, **29**, 554.



Serum-carbon-dioxide content relative to blood-urea nitrogen in various renal diseases.

The second point concerned the vagueness of our definition of renal tubular acidosis—namely, what degree of acidosis is excessive for a particular degree of renal glomerular failure. From a survey of our case-records and of others in our hospital, we find that under stable conditions (including no alkali therapy), in patients with chronic glomerulonephritis, chronic pyelonephritis, nephrosclerosis, and polycystic disease values for serum-carbon-dioxide content are greater than 17 millimoles (mM) per litre with a blood-urea-nitrogen value of 40 mg. per 100 ml., greater than 12 mM per litre at 80 mg. per 100 ml., and greater than 8 mM per litre at 120 mg. per 100 ml. (see figure). The only exceptions, from among 61 determinations in 41 patients, were in 3 patients with chronic pyelonephritis *and* stone. We might speculate that these patients had in fact primary renal tubular acidosis masked as pyelonephritis. In any case, the data from the rest of these patients with diseases that are recognised to produce contracted kidneys with diminished numbers of nephrons and diminished rates of glomerular filtration, provide a control population against which to judge the degree of renal acidosis. By this criterion our patients who were diagnosed as having renal tubular acidosis did exhibit a reduction in serum total CO_2 content that was disproportionate to the level of the blood-urea nitrogen, and, in so far as the latter reflects it, to the impairment of glomerular function.

EDWARD J. HUTH
J. RUSSELL ELKINTON
Philadelphia, Pennsylvania. GEORGE D. WEBSTER, Jr.

CORRELATION OF ANTINUCLEAR ANTIBODIES AND NUCLEAR STAINING PATTERNS

SIR,—In the course of comparing the fluorescent-antibody technique with other methods for detecting antinuclear antibodies, we, like Dr. Beck (June 3), observed different patterns of nuclear staining; our findings were complementary to his.

Previous observations from this laboratory [1] by complement-fixation procedures have demonstrated multiple different antinuclear factors in the serum of patients with lupus erythematosus (L.E.) and related disorders. One of these reacted specifically with antigens contained in the phosphate buffer extract (P.E.) of nuclei, was probably glycoprotein in nature, and was clearly different from the desoxyribonucleoprotein (D.N.A.P.). It seemed of interest to study the nuclear fluorescence of sera containing primarily the P.E. antibodies.

Human kidney sections from fresh frozen material, fixed, after air-drying, in acetone at 4°C for 10 minutes, were the source of antigen. Sera were tested by complement fixation with whole nuclei and with the nuclear fractions D.N.A.P. and P.E. as described above; and for L.E. cell formation by the two-stage method,[2] as well as by immuno-fluorescence. Fluorescent antibody techniques were carried out substantially as described by Coons.[3]

Two contrasting sera were conjugated with fluorescein and used as a basis for inhibition tests; no. 1 with a strongly positive lupus-cell test and complement fixation with D.N.A.P. but not with P.E., and showing whole nuclear staining; and no. 6 with a negative lupus-cell test and complement fixation with P.E. and not with D.N.A.P., and showing speckled staining. Some results obtained are shown in the table.

Two patterns of nuclear staining were distinguishable. One, which in human kidney looks " streaky " and varies in appearance from organ to organ, was clearly the same as Dr. Beck's " speckled " fluorescence; and to avoid duplication we have adopted his term. The other—whole nuclear staining—we

1. Holman, H. R., Deicher, H. R. G., Kunkel, H. G. *Bull. N.Y. Acad. Med.* 1959, **35**, 409.
2. Lachmann, P. J. *Immunology*, 1961, **4**, 142.
3. Coons, A. H. *in* General Cytochemical Methods (edited by J. F. Danielli); p. 399. New York, 1958.

CORRELATION BETWEEN ANTINUCLEAR ANTIBODIES AND NUCLEAR STAINING

Serum no.	Complement fixing inverse titre with			L.E. cell test	Nuclear staining (sandwich technique)	Inhibition by test serum of staining produced by	
	Whole nuclei	D.N.A.P.	P.E.			No. 1 conjugated	No. 6 conjugated
1	64	128	0	+++	Whole nuclei	+	−
2	256	128	0	0	,, ,,	−	−
3	anticomplementary			+++	,, ,,	+	−
4	0	..	..	+++	,, ,,	+	−
5	32	16	32	++	,, ,,	−	−
6	128	0	64	0	Speckled	−	+
7	64	0	128	0	,,	−	+
8	1024	0	512	0	,,	−	+
9	2048	0	2048	±	Speckled and some whole nuclei	−	+
10	1024	256	1024	±	Whole nuclei (speckled after absorption with D.N.A.P.)	−	+

have found less consistent; different sera varied in the degree to which the nuclear membrane was accentuated, and the degree to which the staining was " chromatin-patterned " rather than homogeneous.

It is seen that speckled staining occurred when P.E. was the predominant nuclear antigen reacting with the serum, and that all sera which showed speckled staining inhibited staining by no. 6. On the other hand, whole nuclear staining showed a less specific pattern of reaction; and of the sera showing whole nuclear staining only two others (both also strong lupus-cell formers) inhibited staining by serum no. 1.

To investigate the antigenic specificity of the staining in the two reference sera the following experiments were performed:

(*a*) The fixed sections were treated with desoxyribonuclease (40 μg. per ml. for 90 minutes at 37°C). This treatment virtually abolished the whole nuclear staining by serum no. 1. Much of the staining by serum no. 6 persisted but lost its characteristic morphology—presumably as a consequence of the altered nuclear structure.

(*b*) The fixed sections were treated with *M*/100 sodium periodate for 2 hours at room temperature—a procedure which destroys P.E. in the test tube.[4] This treatment accentuated tissue autofluorescence, but had little effect on whole nuclear staining by serum no. 1. Speckled staining by serum no. 6 was, however, abolished.

(*c*) Absorption of the conjugate with D.N.A.P. abolished staining by serum no. 1 and was without effect on no. 6. Conversely, inhibition with concentrated P.E. abolished staining by no. 6 while staining by no. 1 was unaffected.

We think, therefore, that there is good evidence that P.E. is at least one of the major antigens producing speckled fluorescence. This staining pattern seems to be easily masked and was seen only when anti-P.E. antibody (present in most lupus sera) occurred alone or in great excess. Thus speckled staining is more likely to be found in cases other than " classic lupus ", in which lupus-cell factor and anti-nucleoprotein antibodies tend to dominate. In regard to whole nucleus staining there is evidence that a D.N.A.P. antibody is responsible at least in the case of serum no. 1; and, if the inhibition data are representative, the L.E. cell factor itself may be involved. It seems likely, however, that multiple systems are involved in this sort of staining; and, in view of the variety of antinuclear antibodies especially the components of the D.N.A.P. complex described in L.E., it would be surprising if it were not so.

The Rockefeller Institute, New York 21, N.Y., U.S.A.

P. J. LACHMANN
HENRY G. KUNKEL.

4. Holman, H. A. Personal communication.

MEDICAL ELECTRONICS

SIR,—In an annotation (Aug. 5) you suggested that specialists in electronics might more frequently be invited to address meetings of clinical specialists. Your readers may be interested to know that the Association of Industrial Medical Officers, at their annual provincial meeting in Belfast recently, heard three most interesting and lucid lectures on different aspects of medical electronics. The discussion after these lectures was not only animated but extremely well-informed.

Belfast. JAMES A. SMILEY.

THE ÆTIOLOGY OF RHEUMATOID ARTHRITIS

SIR,—Despite many inquiries no strong genetic or postnatal environmental factors have been found in the ætiology of rheumatoid arthritis. We therefore looked for evidence of congenital factors.

The incidence of some congenital malformations is known to vary with the season of birth, maternal age at birth, and/or birth rank.[1–5] We asked a somewhat different question. Does the season of birth or maternal age influence the incidence of rheumatoid arthritis later in life and hence point to a congenital factor in its ætiology? We think they do. We believe that, if the bias of these factors is not taken into account, expensive field inquiries may be wasted.[6]

Season of Birth

We recorded the birth dates, month and year, of 379 cases of rheumatoid arthritis, and of 758 controls, 2 for each case, matched for year of birth and sex, but with a wide variety of other diseases. The " relative incidence " for each birth month has been calculated. It was found that the relative incidence * per month from September to February was higher than that from March to August. (Mean relative incidence, September–February = 1·19, March–August = 0·81; difference of means = 0·38, $t = 3{\cdot}85$, $P < 0{\cdot}01$).

Maternal Age at Birth

We have collected the details of 107 sibships; the propositi attended our clinics. The data have been examined by the Greenwood-Yule technique.[7 8] The results showed that the incidence of rheumatoid arthritis parallels a rising maternal age at birth; but the association is not wholly convincing. In the analysis rising maternal age seemed to have the greatest influence on those in whom the disease developed at an early age. We therefore analysed [7 8] the first 47 consecutive sibships in which the propositi had developed rheumatoid arthritis before the age of 50, and recorded the index of incidence † of the affected propositi and affected siblings. The maternal age at birth of the affected and unaffected siblings was divided into groups: under 24, 25–, 30–, 35–, and over 40. It was found that there was a steep rise in the index of incidence after the maternal age of 35 (mean incidence up to maternal age of 35 = 0·84. From 35 upwards it was 1·46. Difference of means = 0·62; $t = 11{\cdot}6$; $P < 0{\cdot}01$).

We hope to report this inquiry in detail elsewhere; but in the meantime we wish to thank Prof. T. McKeown and Dr. R. G. Record for helping us with the statistics.

Brook General Hospital, London, S.E.18.
Miller General Hospital, London, S.E.10.

GEOFFREY E. LOXTON
JOAN M. GOLD.

$$\text{* Relative incidence} = \frac{\text{no. of cases}}{\text{no. of controls}} \Big/ \frac{\text{total no. of cases}}{\text{total no. of controls}}$$

$$\text{† Index of incidence} = \frac{\text{no. of cases}}{\text{no. expected}^{7}}$$

1. McKeown, T., Record, R. G. *Lancet*, 1951, i, 192.
2. Record, R. G., McKeown, T. *Brit. Heart J.* 1953, **15**, 376.
3. Record, R. G., Edwards, J. H. *Brit. J. prev. soc. Med.* 1958, **12**, 8.
4. Edwards, J. H. *ibid.* p. 115.
5. Ingalls, T. H. *in* Congenital Malformations (edited by G. E. W. Wolstenholme and Cecilia O'Connor); p. 51. London, 1960.
6. Lawrence, J. S., Laine, V. A. I., de Graaff, R. *Proc. R. Soc. Med.* 1961, **54**, 454.
7. Greenwood, M., Yule, U. *J. R. statist. Soc.* 1914, **77**, 179.
8. McKeown, T., Record, R. G. *Amer. J. hum. Genet.* 1956, **8**, 8.

DRUG ADDICTION

SIR,—The Concise Oxford Dictionary definitions of "addiction" and "habituation" which Dr. Cairns quotes (Aug. 12) give as little idea of their true clinical nature as they do of "maniac": a raving madman; "neurotic": affected with nervous disorder; "hysteric": hysterical fits or convulsions; and—believe it or not—"alcoholic": a powder for staining eyelids. Therefore, if Dr. Cairns disagrees with my definitions (July 22), which are based on over thirty-five years' clinical experience, let him suggest alternatives, because his own experience would enable him to offer something more appropriate than the definitions in the Oxford dictionary.

There are unquestionably more addicts than we think, and it is important to exercise considerable discretion in prescribing drugs which may be habit-forming. The belief, based on official Home Office figures, that we have no serious drug-addiction problem in this country does not warrant complacency but calls for vigilance to ensure that the number of regular drug-takers is kept to a minimum.

However, we must be practical and reasonable and not deny drugs of established therapeutic merit to patients who require them, simply because certain psychopathic types abuse them.

It is no reflection on drugs that "too many people . . . cannot lead 'normal' existences without them". Surely this constitutes one important aspect of therapeutics. The essential difference between patients with addiction as opposed to habituation is that the former cannot lead normal existences even with their drug; surely this is a very good reason for keeping dangerous drugs in a special category.

I have suggested elsewhere [1] that patients who are unwilling to stop taking drugs, who demand higher doses, or who resort to trickery or crime to obtain "adequate" supplies should be referred for full-scale psychiatric investigation.

ELLIS STUNGO
London, W.1. Hon. Secretary, Society for the Study of Addiction.

MANAGEMENT OF THIRD-STAGE COMPLICATIONS IN DOMICILIARY OBSTETRICS

SIR,—Mr. Stabler and Mr. Hunter (Aug. 5) writing independently from Newcastle are each cogently critical of the suggestions of Dr. Fraser and Dr. Tatford (July 15) for modifying the generally accepted procedure for the management by the flying-squad of obstetric third-stage emergencies. Newcastle has a reputation for an independent approach to these matters; and we would like to affirm that our experience in the Liverpool region over the past seven years leads us wholeheartedly to support their criticisms.

The flying-squad here has in that time dealt with 709 cases. Only 6·2% of our patients with third-stage complications were admitted to hospital; in none of those treated at home was there cause to regret this policy. In those patients who were admitted the indication was usually something other than the third-stage complication—e.g., a premature infant. The only death which occurred among the patients treated at home was associated with extreme shock. This patient, who was transfused with 13 pints of blood and 7 bottles of plasma, was never at any time, by any standards, fit for transfer to hospital.

It seems unfortunate that Dr. Fraser and Dr. Tatford chose to base their arguments on the three cases which deteriorated when transferred to hospital. It is true that in each case some part of the regimen which they advised was omitted; but the fact remains that all the patients *were* transferred to hospital and it seems unlikely that deterioration would have occurred had they been treated at home. The assumption that obstetric anæsthesia is safer in hospital than in the home is surely not justified. Parker [1] has pointed out that the reverse may, in fact, be true. The resident anæsthetic registrar is a member of our flying-squad team and he has a full range of equipment, including a portable sucker.

While we can only regard as retrograde the suggestion that patients with retained placentas in domiciliary practice should be transferred to hospital before manual removal, we should like to express our approval of several of the other points raised by Dr. Fraser and Dr. Tatford. The most important of these is the observation that in 34 (33%) of the patients to whom the flying-squad was summoned for third-stage complications, there were specific contraindications to domiciliary confinement. Previous forceps delivery (3 cases) is not an imperative indication for hospital confinement; but even if the figure is reduced to 31 it is still impressive.

Our experience has been similar. In 30% of patients attended by our flying-squad, there were clear contraindications to domiciliary confinement. This points to one of the greatest flaws in our present day maternity services: the patients who most need hospital confinement are often denied this because of either their own folly or the failure of their medical and nursing attendants to exercise proper persuasion. This is a serious but possibly remediable fault. More worrying, however, is the fact that in our hospital experience 67% of postpartum hæmorrhages occur in patients who are otherwise normal and, from an obstetric point of view, apparently suitable for home confinement. Dr. Fraser and Dr. Tatford also note how rarely intravenous ergometrine is given. This depends, at least in part, on whether a doctor is present during or after delivery. In over 25% of cases in our series, the doctor was not at the patient's home when the flying-squad arrived.

Further improvement in the safety of home confinement is likely to be achieved by correction of these two faults.

Department of Obstetrics and Gynæcology, The University, Liverpool.
B. M. HIBBARD
J. S. SCOTT.

SIR,—Now that the discussion on the obstetric flying-squad has been thrown open following the letters of Mr. Stabler and Mr. Hunter (Aug. 5), whose views, apart from probably representing the consensus of opinion, certainly command respect, may I seize upon one point in the original communication by Dr. Fraser and Dr. Tatford:

They have noticed "how few cases of postpartum hæmorrhage have been given intravenous ergometrine by their doctor" prior to their arrival with the obstetric flying-squad. This observation is almost fundamental to the whole problem of third-stage hæmorrhage in domiciliary practice, and is most certainly true. Moreover, it brings to the forefront once again the vexed question whether or not the domiciliary midwife—she it is who is actually confronted by the hæmorrhage, and then calls the family doctor—may administer ergometrine intravenously in case of emergency. The plain fact of the matter is that she is neither expected nor encouraged to do so, and is therefore not equipped accordingly.

The chairman of the Central Midwives Board, participating in a discussion on the uses and abuses of ergometrine at the Royal Society of Medicine on Feb. 27, 1959, stated that "The Board has never said either that venepuncture is outside the province of a midwife or that midwives must be trained to perform venepuncture. The responsibility must be borne by the responsible medical practitioners, and it is up to them to be satisfied that midwives who put needles into veins are competent to do so." This fairly summarises the position in this matter of the Central Midwives Board, which, despite the fact that it is an administrative body, has before now given a lead where the standard of practice is involved.

Positive leadership by the professional bodies concerned is urgently required here. An intravenous injection of

1. Stungo, E. *Med. Pr.* 1961, **144**, 76.

1. Parker, R. D. *Brit. med. J.* 1956, ii, 16.

ergometrine given promptly when a third-stage hæmorrhage is starting, whether the placenta has been delivered or not, will save life and spare anxiety to patient, relatives, and attendants, even if it will not make obstetric flying-squads redundant.

Liverpool, 7. E. G. JONAS.

MOUTH-TO-MOUTH ARTIFICIAL RESPIRATION

SIR,—My one and only effort with this method was made with the short plastic tube on a case of drowning. The accompanying regurgitation from the stomach made it nauseating and finally frustrating, for it was unsuccessful. My suggestion is that it will be in the " dry " case that the result will be most hopeful: dyspnœa in the neonatal infant; electrocution; the cardiac case; the very severe accident; gas-poisoning (carbon monoxide, coal gas, etc.); and even on the operating-table.

Bewdley, Worcestershire. G. S. LAWRENCE.

SERUM-QUININE-OXIDASE

SIR,—In our preliminary communication,[1] we stated that we had confirmed the usefulness of Baier's test [2 3] for serum-quinine-oxidase in the diagnosis of liver-disease.

Subsequent work, on a much larger series of cases, showed raised values of serum quinine oxidase in various conditions. We had therefore some doubts about the accuracy of the test and modified it slightly, as reported in our subsequent letter.[4] Since this did not lead to completely satisfactory results in all cases, the test was suspended and further work was undertaken to check the assumption on which the quinine-oxidase test was based. In the course of this work (the details of which will be published elsewhere) we confirmed the presence of quinine oxidase in rabbit liver with a more refined technique but could find no trace of this enzyme in the liver or spleen in man. We also found that sodium fluoride has a clearing effect on serum and this could explain the results reported in our letter.[4]

We must assume, therefore, that the test described by Baier and carried out in a modified form by us later, is not measuring quinine oxidase in serum, but some non-enzymatic reaction between the serum and quinine hydrochloride. Further work to elucidate this and its possible usefulness as a liver-function test will be required.

Institute of Medical and Veterinary Science, Adelaide, South Australia. W. ROMAN.

A NORADRENALINE-SECRETING CAROTID-BODY-LIKE TUMOUR

SIR,—A recent report of improvement following the removal of a carotid-body tumour [5] and speculation about the presence of aromatic monoamines in specific argentaffin cells in chemoreceptor bodies [6–8] prompts us to record a particularly interesting functional noradrenaline-secreting carotid-body-like tumour.

A twelve-year-old boy had had a painless mass for two years on the left side of the neck at the angle of the jaw. Hypertension, increased to 170/110 mm. Hg by massage of the mass, was noted by the referring physician. The urinary noradrenaline level was 1030 μg., and of 3-methoxy-4-hydroxymandelic acid (vanil-mandelic acid, V.M.A.) 19 mg. per twenty-four hours. At operation the tumour was found near the carotid bifurcation. After removal, the tumour was assayed (including chromatographic analysis); it contained 1·5 mg. of noradrenaline per gramme. No other phenolic amine or hydroxytryptamine derivative was detected. Hypotension followed the removal, and the patient died as a result of cardiac arrest.

On microscopical examination the neoplasm had all the morphological and histochemical characteristics of a carotid-body tumour, including unique ovoid to fusiform argentaffin cells with pseudodendritic processes, predominantly located at the periphery of organoid cell-nests. These cells were identical with those reported in carotid-body tumours and in normal chemoreceptor bodies.[7 8] Moreoever, they contained chromaffin granules and were shown by histochemical tests to be the source of the noradrenaline found on assay.

Evidence from this case, therefore, suggests that the argentaffin cells in carotid-body-like tissue originate from the neural crest and participate in the sympatho-adrenal system, perhaps as a local modulator of baroceptor response [9] or as a noradrenaline store responsive to local or generalised tissue anoxia.[10]

Details of the clinical and pathological features will be presented in the *Archives of Pathology*.

GEORGE G. GLENNER
J. RICHARD CROUT
National Institutes of Health, Bethesda, Maryland, U.S.A. WILLIAM C. ROBERTS.

CANCER RESEARCH IN RHODESIA

Mr. F. G. FEINSTEIN, M.R.C.O.G., writes:

The varied population of Africa provides a vast laboratory for the study of disease and its protean manifestations under different conditions. Not the least interesting is the wide variation in the incidence of different cancers in different areas. The Cancer Association of Rhodesia and Nyasaland wishes to encourage research into the idiosyncrasies of cancer as seen in the Federation. Further information may be obtained personally from its president, Mr. P. Baron, F.R.C.S., c/o Rhodesia House, Strand, London, W.C.2, during September; or alternatively, by writing to Box 3388, Bulawayo, Southern Rhodesia.

Obituary

ALEXANDER MACKENZIE FRASER
M.D. Aberd., F.R.C.P.E., D.P.H.

Dr. A. M. Fraser, secretary and administrative medical officer to the Northern Regional Hospital Board in Scotland, died in Inverness on July 27 at the age of 60.

He was born in 1901 at Kingussie, Inverness-shire. From Kingussie Secondary School he went to the University of Aberdeen, where he qualified M.B. in 1924. After early appointments at the Royal Northern Infirmary, Inverness, and the Royal Aberdeen Hospital for Sick Children he was resident medical officer for three years at the City Fever Hospital, Aberdeen. The stimulating atmosphere of the public-health services at Aberdeen under Matthew Hay and John Parlane Kinloch influenced his future career, and he gave up his original aim of general practice in favour of public health. In 1929 he took the D.P.H. and graduated M.D.

At the age of 28 he became medical officer of health for the burgh and county of Inverness. His administrative skill and natural leadership were soon apparent, and in this post from 1929 to 1948 he played a prominent part in developing the health services under the local authorities and, through the Highlands and Islands Medical Service, in the North of Scotland as a whole; for the authorities with which he was associated were usually persuaded to take the initiative. His contribution to the medical services in the Highlands and Islands was widely recognised, and he was appointed an honorary physician to the King from 1947 to 1950. He was responsible for the foundation in 1946 of the Scottish Council for the Care of Spastics. Westerlea School in Edinburgh was established in 1948 as a result of his untiring efforts, and its success owed much to his zeal and skill. His work for spastics was shared by

1. Roman, W., Dulmanis, A. *Lancet*, 1959, ii, 90.
2. Baier, H., Lang, K. *Biochem. Z.* 1957, **329**, 277.
3. Baier, H. *Klin. Wschr.* 1958, **36**, 569.
4. Roman, W. *Lancet*, 1960, ii, 47.
5. Hunt, T. C. *Proc. R. Soc. Med.* 1961, **54**, 227.
6. Lever, J. D., Lewis, P. R. *J. Physiol.* 1959, **149**, 26.
7. Boyd, J. D. *Brit. med. Bull.* 1961, **17**, 127.
8. Costero, I., Barroso-Moguel, R. *Amer. J. Path.* 1961, **38**, 127.
9. Peterson, L. H., Feigl, E. O., Gouras, P. *J. clin. Invest.* 1960, **39**, 1017.
10. Dripps, R. D., Comroe, J. H., Jr. *Amer. J. med. Sci.* 1944, **208**, 681.

his wife, who was the first warden of Westerlea School. He was elected F.R.C.P.E. in 1957.

R. M. C. writes:

"To his work as secretary and administrative medical officer to the Northern Regional Hospital Board Dr. Fraser brought an intimate knowledge of local medical needs which was invaluable in setting up the new order and in ensuring a balanced provision of specialist services at the main hospitals in Inverness and in the distant parts of a thinly populated and widely dispersed region. It is sad to reflect that he was not able to see completed any of the schemes for new hospitals, which were projected some years ago.

"As an administrator he was readily accessible, and his views on a large range of professional topics were expressed in no hesitant or half-hearted spirit. His mind worked best when fully engaged in promoting new developments, and he brought many to the North in the past thirty years. Temperamentally impatient as he was of prolonged periods of routine, he could enliven the occasion by keeping his arts of advocacy and invective in repair against some favourite King Charles' head. There are many younger doctors at home and abroad who will recall with gratitude that no trouble was too great and no time too inconvenient for helping them forward in their careers.

"Sandy Fraser, as he was commonly called in his native Highlands and far afield, was a genial and robust companion with a rich fund of stories of Highland personalities. He had a wide circle of friends in all walks of life, and he kept the common touch. His help was freely available to friends and acquaintances alike, at times of greater and lesser need. In the local community his interests were general rather than narrowly professional, and he was vice-president of the constituency association of the Liberal Party.

"All his life he was keenly interested in his native Kingussie, and there a large congregation of friends and colleagues took farewell of him, whose stature was greater than life's ordinary measure."

Dr. Fraser leaves a widow and a son.

BARBARA MARTIN MACEWEN

O.B.E., M.D. Edin., M.R.C.O.G., D.P.H.,

AN Edinburgh graduate, Barbara Cunningham qualified in 1901 and took a diploma in midwifery at the Rotunda in 1902. After some years in India, where she worked at the Dufferin Hospital, Nagpore, she returned to take her Edinburgh doctorate in 1909 and the Cambridge D.P.H. in 1910. She worked as assistant M.O.H. and inspector of midwives in Manchester until she became a medical officer with the National Insurance Commission, and at the Ministry of Health soon after its formation. In 1925, on her marriage to Dr. Hugh Macewen, she retired from the Ministry; but she went back to it later to help in the big inquiry into maternal mortality of the early '30s, and she obtained her M.R.C.O.G. in 1937. She again returned at the outbreak of war, but retired with her husband from the Ministry in 1941. After two years at Ulverston, where her husband was acting M.O.H., they went to Ballochmyle Hospital in Ayrshire, of which he was the medical superintendent, until his final retirement to Innellan on the Clyde. After her husband's death in 1955 she lived in Edinburgh.

A colleague writes:

I was closely associated with Barbara Macewen when she came back to the Ministry of Health after her marriage, to be the moving spirit in the Inquiry into Maternal Mortality, of which the report was published in 1937.

Tall and rather gaunt, with a formidable tongue and an exceptional devotion to her work in all its details—how annoyed she would have been at the mis-spelling of her name in her obituary notice in a daily paper!—she was regarded by more casual mortals with apprehension and awe. But she could disarm the most hostile by her warm-heartedness and wit. I remember during the inquiry the clerk to a certain county council received us by throwing himself back in his chair and asking in a most unfriendly tone, "Well, Dr. Macewen, and what have you found in *my* County?" "A great deal of kindness and courtesy, Mr. Clerk," was the reply, soon after which he was asking her to lunch at his home!

NORMAN JOLLIFFE

M.D. New York, F.A.C.P.

SINCE 1949 Dr. Jolliffe had been director of the bureau of nutrition of the New York City department of health, and he was widely known as a nutritionist.

A West Virginian, he graduated in medicine at New York University in 1926 and six years later became chief of the medical service of the psychiatric division at Bellevue Hospital. During the war he joined a Washington committee on nutrition, in which he worked for the enrichment of white flour and bread, and after the war he opened the first nutrition clinic of the New York health department. He was co-editor of a textbook, *Clinical Nutrition*, published in 1950, and wrote for the public, in 1952, a book on weight reduction which became a best-seller.

Dr. Jolliffe was a member of an international group which surveyed the nutritional needs of Newfoundland in 1944 and 1948, and in 1951 he advised the public-health authorities of São Paulo, Brazil, on aspects of their diet-enrichment programme. He paid two visits to Rome at the invitation of the Centro per lo Studie dell'Alimentazione Infantile, and in 1954 he participated in a nutritional survey in Formosa. In 1955 he received the Carlos Finlay award of the Cuban Government in recognition of his nutritional study of Cuban schoolchildren. From 1952 to 1954 he was president of the National Foundation.

In the New York department of health, he originated in 1957 a study of the relation between diet and heart-disease, which depends on an Anti-Coronary Club. Members of the club—men between the age of 50 and 59—follow prepared diets and are periodically examined. Though the study has several years still to run, it has already confirmed that, with a suitable diet, the blood-cholesterol can be kept at a lower level.

Last February, Dr. Jolliffe received from New York University its Presidential citation—the highest honour it gives to an alumnus. He had lost his sight several years ago, and had been ill for a long time; but he continued to work until his death on Aug. 1 at the age of 59.

Appointments

DOYLE, J. O., M.D. N.U.I., M.R.C.P.I.: consultant in venereal diseases, Huddersfield/Halifax area.

EDWARDS, C. O., M.B. Cantab., M.R.C.P.: consultant chest physician, Kingston and Mortlake chest clinic areas.

FOSTER, E. J. H., M.B. Manc., D.P.H., D.OBST.: senior assistant divisional M.O., area adjacent to Oldham.

MEADOWS, J. G., M.B. Brist., D.P.H.: assistant county M.O., Dorset.

MURRAY, I. H. F., M.B. St. And.: trainee medical superintendent attached to the Northern Regional Hospital Board of Scotland.

ROBERTS, PHYLLIDA M. M., M.D. Lond., D.PATH., D.T.M. & H.: consultant pathologist, Elizabeth Garrett Anderson Hospital, London.

STEWART, I. M., M.B. St. And., F.R.C.S.E.: consultant orthopædic surgeon, Law Hospital, Carluke.

Births, Marriages, Deaths

BIRTHS

JAGO.—On Aug. 5, at the Nuffield Maternity Home, Oxford, to Margaret Jago, wife of Douglas Hewitt—a son.

Notes and News

REMUNERATION IN THE N.H.S.

THE pause in wage and salary increases which the Chancellor of the Exchequer is applying in the Civil Service is to be applied, on the same principles, to those engaged in the National Health Service. The Ministry of Health, in a letter to the chairmen of the management and staff sides of N.H.S. Whitley councils, sets out these principles as follows:

(*a*) Commitments for pay increases already entered into will be met. This includes agreements already reached, awards made or awaited in cases already taken to arbitration, and firm offers already made. These increases will be put into effect with whatever operative date has been agreed, awarded, or offered.

(*b*) For the rest, the existing negotiating machinery will continue to function, and claims will be considered on their merits, but during the period of the pause any offer of increased pay which it may be thought reasonable to make will generally be for future implementation (with no retrospection) when circumstances permit.

(*c*) In the event of arbitration the Government will withdraw from the scope of arbitration, and retain in its own control the timing (and, if necessary, the staging) of the putting of an award into effect.

(*d*) These arrangements will also apply to claims for improvement in conditions of service other than pay.

(*e*) The Government has it in mind to review the situation early next year.

A LION AMONG LIONS

LIKE his sparring partner George Bernard Shaw, Sir Almroth Wright was born under Leo. So Brigadier L. R. S. MacFarlane, director of pathology, War Office, reminded a distinguished audience in an address at the Royal Army Medical College, Millbank, on Aug. 10. Though gentler than Shaw, Wright could roar as loudly.

It is fitting that the centenary of this great medical scientist should be marked by the R.A.M.C., for he was given the chair of pathology at the Army Medical School when he was 31. In the ten years he was at Netley he taught Leishman, Lyle Cummins, S. R. Douglas, Semple, Harvey, Leonard Rogers, L. W. Harrison, and many others famous in pathology. As his teaching was part-time, he had leisure for research, and all the important work on anti-typhoid inoculation was done at Netley. In 1896 he reported [1] how he had inoculated two young volunteers, surgeons on probation, although the War Office frowned on officers taking such part in his work. His relations with his loyal juniors were always better than with his seniors, for he used his waspish tongue against any authority that seemed to him wrong or obstructive. When he moved to St. Mary's Hospital in 1902, the explanation given by the War Minister was that, because his duties there and at "the Medical Staff College" were incompatible, he had resigned from Netley. This was only a few years before the college moved to Millbank, removing any geographical difficulty. Wright continued to campaign for typhoid inoculation, and when Kitchener made this compulsory, in the first world war, the department at St. Mary's was devoted to making vaccine. Its effect justified all Wright's efforts, and its value has remained largely undisputed.

During the war, Wright went as a colonel to Boulogne and worked with Fleming on the physiology of wounds. He was officially consulting physician in France and he angered his chief, General Sloggett, by preparing a memorandum outrageously critical of the medical services of the Army in France. He sent copies of this to everyone from Lloyd George downwards, and yet ignored the usual channels. Sloggett ordered him to resign his commission, but the order was countermanded by the War Minister, Lord Derby. Brigadier MacFarlane skilfully completed the picture of Wright as a fiery but gentle Irishman, humorous yet always fighting for the truth.

Lieutenant-General H. E. Knott, director-general of Army Medical Services, then asked Mr. Dickson Wright to speak. Mr. Dickson Wright, a distant relative, said that the lecture had evoked a vivid nostalgia and a great hope: perhaps one day disease might be conquered not by the artifice of chemotherapy but by eliciting the natural powers of immunity. Then Wright would indeed triumph.

1. *Lancet*, 1896, ii, 807.

MEDICINE FOR THE LAYMAN—AND DOCTOR

THE trouble with most popular books on human biology is not that they are popular but that they are bad. This is not altogether surprising, for the human body is the most complicated of all biological machines—quite unsuited, one would have thought, to being used as an introduction to elementary science. But used it is. Professional scientists tend to adopt one of two methods. Some oversimplify until their subject's last spark of βίος is extinguished. Others generate a romantic haze in which the most prosaic of physiological functions become either "mysteries" or, more often, "miracles". But either method is preferable to the fashionable journalistic approach which skips all fundamentals and examines "current concepts" (most of them revolutionary) as illuminated by the personalities of their proponents. ("Academic diehards may grumble about his 'experimental evidence'; but Prof. X, explaining to us his revolutionary rejuvenation theory, left no doubts in *our* minds. His exposition was as sparkling as the hock—which his charming collaborator, Miss Y, served with the Tournedos Chasseur—was still: all the evidence we needed shone in their eyes . . ." "Dr. Z had that deep *dedicated* look of the true pioneer surgeon: watching his firm grip around the neck of the decanter, dry mortality statistics faded into insignificance . . . " [1]).

And yet, that the task is not beyond the power of man—or at least of man and woman—is now conclusively proved by Benjamin Miller and Ruth Goode.[2] The publishers somewhat surprisingly claim that theirs is the first "authoritative, up-to-date, and comprehensive" popular book on the human body; but one only wishes that it were. It is certainly a little masterpiece. Written in plain, elegant English, the text does more than instruct and entertain: it fires the imagination. Doctors, who should buy the book for their schoolboy son, daughter, wife, father-in-law, grandmother (or whoever's birthday comes next), must not fail to dip into its pages first. They will probably be reluctant to part with it.

THE SYNDROME OF THE GASES

MANY of those who specialise in disorders of the digestive system will have noticed that the word "gases" is used very commonly by patients from the East. In describing their symptoms the first word they utter is very often "gas"; and, though this may convey little to the consultant, it means a great deal to the patient. It is a complaint more common in middle-aged men than in women.

While under examination, the patient may eructate very noticeably. The epigastrium is distended and borborygmi audible, but radiography does not afford much information. The question is why these people should have this distension, not only of their stomachs but of the whole digestive system. Is it simply an expression of maldigestion of starch, cellulose, and other material, or can it be related to their state of mind? Usually they are overweight, indolent, and averse to exercise: they consume large amounts of cereals, sweetmeats, and vegetables, and drive around in high-powered cars.

In Pakistan the inhabitants of Karachi designate the condition "Karachi tummy", and some link it up with the inevitable amœbiasis; but it is aggravated rather than relieved by antiamœbic drugs. Others quote the old saying that "the people of Karachi are awake when they are asleep and they sleep when they are awake"; from which they infer that their gut becomes lethargic too. But "gas" is by no means confined to Karachi, or indeed Pakistan, but is common throughout the East.

In discussing its origin Lieut.-Colonel M. H. Shah [3] lays emphasis on the enlargement of the liver, and recalls the term "tropical liver" of our forefathers. Yet when all the infective,

1. References by special request.
2. Mind and Body. By B. F. MILLER, M.D., and RUTH GOODE. London: Gollancz. 1961. Pp. 375. 21s.
3. *J. Pakistan med. Ass.* February, 1961.

allergic, dietetic, and climatic possibilities have been considered, there is much to be said for the psychomatic, with the abdomen as sounding-board of the emotions. The simplest explanation is that people eat far too much, think far too much about their food, brood over their digestions, and take no exercise; and they would usually benefit most from a walking-tour on short rations.

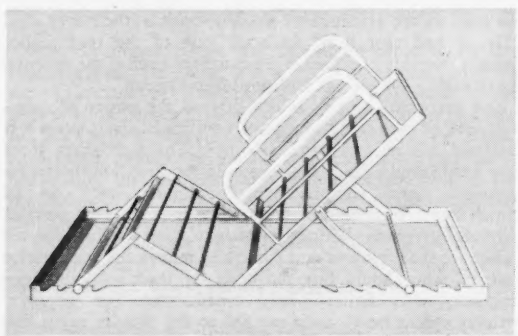
HEARING-AIDS

IN a valuable new booklet [1] the National Institute for the Deaf sets out general advice for those who are thinking of acquiring a hearing-aid or changing an aid for a better one, or who are having trouble with an aid. Specific advice will be given to members of the public who apply to the secretary of the institute, 105, Gower Street, London, W.C.1.

A BED-REST FOR CHILDREN

Dr. Cicely Williams writes from the School of Public Health in Beirut (Lebanon):

" The bed-rest illustrated, devised by a nursing sister (Miss Sim), was made in two sizes by a local metalwork firm, and was first used in the children's wards of the General Hospital, Singapore, in 1936–42. Back and leg pieces can be altered to any angle, or laid



flat. Pillows can be arranged on the rest according to the size of the patient, and covered with a waterproof cover and then a sheet. The patient and the pillows keep easily in place, and do not slip into uncomfortable positions. Beds can be made swiftly, as there is no call for changing pillowcases. The child is lifted bodily, and the sheet and waterproof cover changed in a matter of moments.

" This bed-rest seems to supply the greatest comfort with the least restraint for the patient. It is, of course, particularly useful for chest cases, beriberi, and all forms of severe malnutrition, and other hospitals might like to try it."

Future of the Mental Hospital

A symposium on this subject for consultant psychiatrists is to be held on Oct. 5 and 6, at the Institute of Psychiatry, Maudsley Hospital, Denmark Hill, London, S.E.5. The speakers will be Dr. G. C. Tooth, Dr. J. A. Scott, Prof. Thomas McKeown, Dr. J. K. Wing, Prof. Llewelyn Davies, Dr. John Tizard, and Mr. W. A. J. Farndale. Applications to attend should be sent to the dean at the institute before Sept. 15.

1. *Hearing Aids.* Pp. 17. 6*d*.

University of Oxford

Prof. G. W. Harris has been appointed to the Dr. Lee's chair of anatomy from Oct. 1, 1962. He is to succeed Sir Wilfrid Le Gros Clark, who has held the chair since 1934.

Professor Harris, who is 48 years of age, graduated B.A. at Cambridge in 1936, and qualified M.B. from St. Mary's Hospital, London, three years later. He graduated M.D. in 1944 and SC.D. in 1950. From 1940 to 1948 he was successively university demonstrator and lecturer in anatomy at Cambridge; and from 1948 to 1951 he was lecturer in physiology. In 1950, with a Rockefeller Foundation grant, he visited university departments in the U.S.A. and was also Claude Bernard visiting professor in the University of Montreal. In 1952 he was appointed senior lecturer in experimental neuro-endocrinology at the Institute of Psychiatry in the University of London, and later that year took up his present appointment as Fitzmary professor of physiology at the institute. In 1953 he was visiting professor of anatomy at the University of California, Los Angeles, and was later appointed visiting professor of anatomy for six months at the University of California, San Francisco. He was active in the formation of the Scientific Publications Council, of which he was the first chairman. He is an executive member of the International Brain Research Organisation, sponsored by UNESCO. He was elected F.R.S. in 1953. Professor Harris's research work has been concerned with the anatomy and physiology of the hypophysis and the nervous control of pituitary secretions.

University of London

Mr. B. N. Catchpole has been appointed reader in surgery at St. Bartholomew's Hospital Medical College, and Dr. J. C. G. Coleridge reader in physiology at the Royal Free Hospital School of Medicine.

On Tuesday, Aug. 22, at 5 P.M., at the London Hospital Medical College, Turner Street, E.1, Prof. G. de Takats, of the University of Illinois College of Medicine, will speak on intermittent claudication.

Royal College of Physicians of London

Sir Arthur Thomson will give a Harveian oration on Wednesday, Oct. 18, at 3 P.M., at the college, Pall Mall East, S.W.1. He will speak on the Consummation of William Harvey.

International Society of Surgery

The nineteenth congress of this society will be held in Dublin from Sept. 2 to 9. Particulars may be had from Prof. Lambert Rogers, F.R.C.S., Royal Infirmary, Cardiff.

Horse Shoe Club

The annual general meeting of this club, founded in 1932, was held recently at the Ciba Foundation in London. The chief aim of the club is to foster friendship between the United States, Canada, and Great Britain. Canadian and American sections have been formed. Since 1936 the club has arranged yearly exchanges of British doctors—recently of surgeons—through the cooperation of the American College of Surgeons since 1956, their places being taken in this country by American surgeons. The club works closely with the Nuffield Foundation, the Ciba Foundation, and the English Speaking Union, and, since its formation, with the Anglo-American Medical Society. Further details may be had from the honorary secretary, Dr. Claude S. Nicol, St. Bartholomew's Hospital, London, E.C.1.

Sir Harry Platt is to visit Australia and New Zealand in November and December at the invitation of the Royal Australasian College of Surgeons, and will take part in ceremonies connected with the launching of an appeal by the college for funds to support and extend its postgraduate activities. Lord Casey is chairman of the college appeal committee.

On Tuesday, Aug. 22, Dr. John C. Beck, of Montreal, will speak on metabolic effects of growth hormone in man; and, on Wednesday, Aug. 23, Dr. A. G. Bearn, of New York, on genetics in clinical medicine. Both lectures will be given at 5.15 P.M. at the Royal Free Hospital, Gray's Inn Road, London, W.C.1.

An appeal on behalf of UFAW (the Universities Federation for Animal Welfare) will be broadcast on the B.B.C. Home Service at 8.25 P.M. on Sunday, Aug. 27, by Mr. Sydney Jennings, president of the British Veterinary Association.